Original article

J Korean Soc Pediatr Nephrol 2013;17:86-91
DOI: http://dx.doi.org/10.3339/jkspn.2013.17.2.86

ISSN 1226-5292 (print)
ISSN 2234-4209 (online)

가와사키 질환에서의 신증상과 영상 검사 소견

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Renal Manifestations and Imaging Studies of Kawasaki Disease

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Received: 20 September 2013
Revised: 4 October 2013
Accepted: 8 October 2013

Purpose: The aim of this study was to verify renal inflammation following Kawasaki disease (KD) using single photon emission computed tomography along with Technetium-99m dimercaptosuccinic acid scintigraphy (DMSA renal SPECT).
Methods: From March 2011 to October 2011, 15 patients diagnosed with KD at the National Health Insurance System Ilsan Hospital were enrolled in the study. All patients underwent DMSA renal SPECT to evaluate renal involvement during the acute phase of KD. Urine β2-microglobulin (β2-MG), a marker of renal proximal tubular dysfunction, was also measured to assess renal damage.
Results: All 15 patients had normal renal function test results. However, microscopic hematuria and pyuria were observed in 13% and 33% of the patients, respectively. Moreover, urine β2-MG was elevated in 46% of the patients. In addition, patients were divided into two groups based on β2-MG level: those with an increased β2-MG level, and those with a normal β2-MG level. No significant differences were found between these two groups in clinical characteristics, laboratory, sonography, and echocardiography findings. All patients' DMSA renal SPECT scans were normal.
Conclusion: Our study showed that mild abnormalities in the urinalysis and elevated urine β2-MG were the only findings of renal involvement in KD. However, no aggressive renal manifestations were detected on DMSA renal SPECT.

Key words: Kawasaki disease, Renal complication, Single photon emission computed tomography together with Technetium-99m dimercaptosuccinic acid scintigraphy (DMSA), β_2-microglobulin

Introduction

Kawasaki disease (KD) is an acute systemic vasculitis of unknown etiology in children [1]. The most affected age group of KD is younger than

five years old [2]. This syndrome is diagnosed based on the following clinical criteria: persistent fever for at least five days and four of five features-rash, conjunctival injection, changes of lips or oral mucosa, erythema and swelling of hands and feet, and lymphadenopathy [3, 4]. The most common and serious complication is the coronary artery dilatation, which peaks at four to six weeks after developing KD. However, it is known that if intravenous immunoglobulin (IVIG) and high-dosage aspirin were administered within 10 days, only 5% of the patients were affected by coronary artery complications [5, 6]. Genitourinary involvements are rare complications in KD. The most common findings are proteinuria and sterile pyuria, and microscopic hematuria was observed in fewer patients with KD [7, 8]. Although rare, critical sequellae, such as interstitial nephritis, hemolytic uremic syndrome, nephrotic syndrome, acute renal failure, and renovascular hypertension, have been reported [9, 10].

However, previous reports about renal involvement of KD have been studied by only clinical manifestations and laboratory findings, and have not been evaluated systematically. Also, to our knowledge, there were only a few reports using ultrasonography as an imaging modality to confirm renal damage, and only one study has been reported from Wang JN, et al. using single photon emission computed tomography together with Technetium-99m dimercaptosuccinic acid scintigraphy (DMSA renal SPECT), highly sensitive and specific modality for detecting renal inflammatory scars in KD patients. They found that a significantly high ratio of the patients who suffered from KD showed renal inflammatory foci in DMSA renal SPECT, which suggested a possibility of renal scar formation subsequent to KD [11].

Because of the rarity of the imaging investigations of the renal involvement of KD, the patients who were diagnosed KD at our institution went through DMSA renal SPECT to confirm the inflammation and scar of the kidney.

Additionally, using urine β2-microgloulin (β2-MG), indicating renal tubular damage marker, we investigated origins of proteinuria and the possibility of renal parenchymal injury in KD patients.

Materials and methods

1. Patient selection

From March 2011 to October 2011, patients admitted to National Health Insurance Service Ilsan Hospital with febrile KD were recruited as candidates for this prospective study. KD was defined based on the standard diagnostic criteria : persistent fever for at least five days and four of five features-rash, conjunctival injection, changes of lips or oral mucosa, erythema and swelling of hands and feet, and lymphadenopathy [3, 4]. The exclusive criteria were history of urinary tract infection, positive results from urine culture at initial diagnosis, or other urogenital abnormality. The patients who signed the informed consent, which was approved by the Institutional review board, were enrolled in the study.

2. Data collection

All of the patients were initially treated with 2 g/kg of IVIG and 100 mg/kg of aspirin orally. When fever was subsided, patients were given 5 mg/kg of low-dose aspirin. Laboratory and urinalysis data of all patients were collected at 1st hospitalization day. Complete blood cell counts, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) were included in laboratory data. White blood cell (WBC) count of 4000/μL to 10,000/μL was considered as a normal range. CRP level of over 8 mg/L was considered as a positive for inflammation. To evaluate renal function, blood urea nitrogen (BUN) and creatinine were measured. Creatinine level over 0.4 mg/dL for patients younger than 12 months and creatinine level over 0.7 mg/dL for patients older than 12 months were considered as having renal problems. Aspartate aminotransferase (AST) level over 45 U/L or alanine aminotransferase (ALT) level over 45 U/L were considered as hepatitis. Hypoalbuminemia was considered if albumin level was under 4.0 g/dL. Hyponatremia was defined as sodium level below 135 mmol/L. Also, urine β2-MG, a renal tubular damage marker, was considered as presence with renal tubular damage if urine β2-MG level was over 0.25 mg/L. Pyuria was

diagnosed if urinalysis presented the white blood cell count >10 per high power field and hematuria if the red blood cell count >5 per high power field.

An ultrasonography (USG) was done to exclude renal mass or congenital urogenital anomaly. Also, DMSA renal SPECT was done to evaluate renal involvement during the acute phase of KD. The images of DMSA renal SPECT were officially reviewed by a board-certified nuclear medicine doctor. Renal inflammation was diagnosed if the image presented either decreased focal uptake or diffused diminished DMSA uptake.

Echocardiography was also performed during the acute phase of KD by a pediatric cardiologist. If the diameter of coronary artery was over 3 mm for patients under 5 years old or over 4 mm for patients over 5 years old, those patients were diagnosed as having coronary artery dilatation. The patients who showed coronary artery dilatation underwent follow-up echocardiography after eight weeks.

3. Statistical analysis

Continuous data was analyzed as mean±standard derating, and differences between groups were analyzed by Mann-Whitney U test. For <15 cases, categorical data was analyzed by Fisher's exact test with IBM SPSS version 20.0. (IBM Co., Armonk, NY, USA) for statistics. All values with $P<0.05$ were considered as statistically significant.

Results

A total of 15 patients were enrolled in this study. The study population consisted of 12 boys (80%) and three girls (20%). Mean age was 4.5±2.69 years old (range, 2 to 11 years) at the time of initial diagnosis. From the first day of fever development until the first day of admission, average duration of fever was 6.2 days (range, 5 to 8 days). Among the 15 patients, fever subsided after administering IVIG in 13 (87%) patients. In the remaining two patients, fever was subsided in the second administration of IVIG. None of the patients presented hypertension, oliguria, or polyuria.

Leukocytosis was observed in 13 patients (87%). Only one patient presented leukopenia, and the other one stayed in normal range (mean 15,680±7,336/mm^3). ESR was elevated in all of the patients (48.1±25.2/mm^3). Thirteen patients (87%) showed an increased CRP level (mean 6.6±6.2 mg/L). ALT was elevated in eight (53%) patients (mean 85.5±96.0 IU/L). Hypoalbuminemia was observed in 14 (93%) patients (mean 3.54±0.45 g/dL), and one of them presented marked hypoalbuminemia (2.2 mg/dL). There were three patients (19%) who showed hyponatremia (mean 135.9±2.9 mmol/L). All of the patients presented normal renal function tests. In urinalysis, microscopic hematuria and pyuria were observed in two patients (13%) and five patients (33%) respectively. β2-MG was measured in 13 patients and six (46%) of them showed elevated levels (mean 1.40±3.95 mg/g creatinine).

Echocardiography showed a coronary artery aneurysm in five patients (33%). Only one patient presented remnant coronary artery dilatation at the follow-up echocardiography performed eight weeks later. The initial USG revealed liver or gallbladder abnormality in three patients (20%, 1 case diffuse liver disease, 1 case mild hepatomegaly, 1 case distended gallbladder). However, none of the patients showed pathologic findings in the kidney. No significant findings were observed in DMSA renal SPECT in all of the patients (Table 1).

The patients were divided into two groups with an increase in β2-MG levels and with normal range of β2-MG. The comparison between the two groups showed no significant differences in clinical characteristics, laboratory findings, USG, and echocardiography findings (Table 2).

Discussion

KD is known for its systemic involvement in forms of vasculitis. Therefore, entire organs are susceptible, and the kidney is one of them since it mostly consists of vascular structure. Nevertheless, there are only a few reports regarding kidney involvement in KD. Most of the studies have reported that clinical manifestation of kidney involvement in KD is temporary urethritis or meatitis [12]. However, as diagnostic tools have advanced recently, interest has

Table 1. Clinical Characteristics of Patients with Kawasaki Disease (N=15)

Patient Sex/Age (yrs)	Urine β2-MG* (mg/L)	Abdominal-sonography	DMSA-SPECT	Echocardiography
M/7	not checked	normal	normal	normal
M/4	14.50	normal	normal	coronary dilatation
M/3	0.29	hepatomegaly	normal	coronary dilatation
M/5	1.06	normal	normal	normal
M/4	0.95	distended gallbladder	normal	coronary dilatation
M/2	0.22	normal	normal	normal
M/4	0.33	normal	normal	coronary dilatation
M/2	0.06	normal	normal	normal
M/2	0.05	normal	normal	normal
M/3	0.39	normal	normal	normal
M/11	0.22	normal	normal	normal
M/2	0.11	normal	normal	coronary dilatation
F/9	not checked	diffuse liver disease	normal	normal
F/6	0.01	normal	normal	normal
F/4	0.11	normal	normal	normal

*β2-MG, β2-microglobulin

Table 2. Comparison of Laboratory and Echocardiologic Findings by β2-macroglobulin Levels

β2-microglobulin	<0.25 (N=7) (mg/L)	≥0.25 (N=6) (mg/L)	*P*-value
Age (year, mean±SD)	4.14±3.39	3.83±0.75	0.821
Gender			0.743
Male (%)	5 (71.4)	6 (100)	
Female (%)	2 (29.6)	0 (0)	
White blood cell count (/μL)	14,657±6,588	19,200±7,468	0.253
Hemoglobin (g/dL)	11.7±1.5	11.6±0.98	0.775
Albumin (g/dL)	3.7±0.3	3.5±0.64	0.772
Serum BUN (mg/dL)	10.13±4.35	9.8±3.69	0.775
Serum creatinine (mg/dL)	0.34±0.12	0.44±0.09	0.116
AST (IU/L)	60.43±59.7	130.17±53.91	0.153
ALT (IU/L)	75.57±78.18	186.5±105.21	0.617
Na (serum, mmol/L)	135±3.73	136.5±2.43	0.942
ESR (mm/H)	54.29±25.15	52.83±20.61	0.886
CRP (mg/L)	5.31±6.81	8.25±6.41	0.086
Urinalysis			
Pyuria (%)	5 (71.4)	3 (50.0)	0.267
Hematuria (%)	0 (0)	1 (16.7)	0.462
Echocardiography			0.103
Normal (%)	6 (85.7)	20 (33.3)	
Abnormal (%)	1 (14.3)	4 (66.7)	

Values are mean±standard deviation.
Abbreviations: BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

developed for long-term complications and prognosis involving the kidney in KD. Even though there were no such clinical symptoms in our study, recent case reports have presented acute renal failure, hemolytic uremic syndrome, and interstitial nephritis as kidney involvement in KD [9, 13, 16].

However, renal involvement in KD patients is mostly subclinical pyuria, which makes it very hard to identify its origin. To investigate origins of pyuria in KD patients, there are reports that support the possibility of KD's renal parenchymal involvement by renal biopsy or postmortem autopsy. Histological findings have shown expansion of mesangial matrix, tubular necrosis, interstitial infiltration of lymphocytes, plasmocytes, and eosinophils [10, 14, 17]. In 2007, Watanabe, et al. studied the origin of the urinary leukocytes in KD patients with

pyuria using transcatheterization when collecting urine. The study compared voiding urine with urine that was obtained by transcatheterization [18]. The results showed elevated BUN, creatinine, and β2-MG levels in the group with pyuria from the bladder, which was obtained in urine by transcatheterization. From the results, the author postulated some patients with KD develop sterile pyuria as a result of mild and subclinical renal injury. Our study also concluded that pyuria was the most common form of symptoms (33%). Hematuria was observed in two patients (13%).

Since this study did not use the transcatheterization technique to collect urine, we do not know the pyuria was due to urethritis or caused by renal injury. For this purpose, β2-MG level, a marker of renal proximal tubular damage [19, 20], was compared, but did not show any statistically significant difference between the pyuria and non-pyuria group. None of them presented with elevated BUN and creatinine levels. However, six (46 %) out of 13 patients showed elevated β2-MG levels, which indicates renal parenchymal involvement, such as interstitial nephritis. This finding also coincides with previous reports[7]. A recent publication reported that hyponatremia is related to severe KD [21, 22]. Watanabe et al. presented among 114 patients with KD; 51 patients (44.7%) had hyponatremia, and coronary artery lesions and hepatitis were significantly more common in patients with hyponatremia. Additionally, pyuria and hematuria were present significantly more often in patients with hyponatremia [23]. However, our study results did not find any of significant increase of coronary artery dilatation (P=0.242), pyuria (P=0.659), or hematuria (P=0.371) in those who presented hyponatremia.

Our radiologic study using sonography and DMSA renal SPECT also showed differences from previous study. According to a study by Nadri et al., four out of seven patients presented enlarged, swollen kidneys with increased cortico-medullary differentiation in kidney USG, which was compatible with renal vasculitis[24]. However, regardless of urinalysis results, all 15 patients in our study presented normal in kidney USG.

Recently, Wang et al. reported a study using DMSA renal SPECT among KD patients. From this study, the author found that 26 out of 50 patients (52%) presented kidney parenchymal scarring formation, indicating renal involvement of KD[11]. The result of the study implicated that long-term follow-up was necessary to control possible long-term sequellae, such as renal hypertension. On the contrary, none of our patients showed abnormalities in DMSA renal SPECT.

There are a few limitations in our study. Due to the small number of the study population, selection bias is a possibility. Also, there should be long-term follow-ups to clarify the course of disease. Finally, catheterization of urine collection might increase accuracy of the study.

In conclusion, our study exhibited that mild abnormalities in the urinalysis and elevated β2-MG were the only findings of renal involvement in KD. However, there were no aggressive renal manifestations detected in DMSA renal SPECT.

Acknowledgments

This study was supported by Research Grant from the NHIS Ilsan Hospital.

This article was poster presented at the 16th congress of the International Pediatiric Nephrology Association in Shanghai, China.

한글요약

목적: 본 연구는 가와사키 질환의 신장 침범에 대하여 비교적 덜 침습적이며, 특이도와 민감도가 높은 검사인 Technetium-99m dimercaptosuccinic acid scintigraphy (DMSA renal SPECT)을 통하여 밝혀보고자 한다.

방법: 2011년 3월부터 10월까지 국민건강보험 일산병원에서 가와사키로 진단된 15명의 환아들을 대상으로 진행하였다. 15명의 환아 모두 가와사키의 급성기에 DMSA renal SPECT를 시행하였다. 또한 신장 세뇨관 손상 지표인 요중 β2-microglobulin (β2-MG)을 측정하여 이를 통한 가와사키 환아에서 신장 손상의 조기 진단 가능 여부를 연구해보았다.

결과: 환아 15명 모두의 신기능 검사는 정상이었다. 소변검사상 현미경적 혈뇨와 농뇨가 각각 13%, 33%에서 관찰

되었다. 요중 β2-MG는 46%에서 증가된 소견을 보였다. 또한 환아들을 요중 β2MG를 기준으로 증가되어 있는 군과 증가되지 않은 군으로 나누어 비교, 분석해 보았으며, 두군간에 임상 증상, 임상 검사, 초음파 검사 및 심초음파 검사에서 유의한 차이를 보이지 않았다. 모든 환아에서 DMSA renal SPECT는 정상 소견을 보였다.

결론: 본 연구에서 가와사키 질환의 신장 침범은 경한 소변 검사 이상 및 일부 환아에서의 요중 β2-MG의 상승 소견을 보였으며, DMSA renal SPECT에서 관찰될 정도의 신장 침범은 보이지 않았다.

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