Pediatr Infect Vaccine. 2018 Dec;25(3):148-155
https://doi.org/10.14776/piv.2018.25.e11
pISSN 2384-1079·eISSN 2384-1087

PIV PEDIATRIC INFECTION & VACCINE

Original Article

Clinical Significance of the Bacille Calmette-Guérin Site Reaction in Kawasaki Disease Patients Aged Less than 18 Months

Sung Hyeon Park, Jeong Jin Yu, Jihye You, Mi Jin Kim, Eun Jung Shin, Hyun Ok Jun, Jae Suk Baek, Young-Hwue Kim, Jae-Kon Ko

Department of Pediatrics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, the Republic of Korea

Received: Jul 29, 2018
Revised: Sep 9, 2018
Accepted: Sep 18, 2018

Correspondence to
Jeong Jin Yu
Division of Pediatric Cardiology, Department of Pediatrics, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, the Republic of Korea.
E-mail: jjyu@amc.seoul.kr

ORCID iDs
Sung Hyeon Park
https://orcid.org/0000-0002-1991-9207
Jeong Jin Yu
https://orcid.org/0000-0003-1601-3685

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

ABSTRACT

Purpose: The purpose of this study was to investigate the clinical significance of Bacille Calmette-Guérin (BCG) site reaction in terms of diagnosis and outcome prediction in young children with Kawasaki disease (KD).
Methods: The incidence of BCG site reaction in the respective age ranges was investigated in 1,058 patients who were admitted at Asan Medical Center between January 2006 and February 2017. The 416 patients under 18 months of age were enrolled as subjects for the analysis of the association between BCG site reaction and other laboratory and clinical findings. The analysis was performed separately in complete and incomplete KD groups.
Results: The incidence rate of BCG site reaction was peaked at 6–12 months (83%) and decreased with increasing age after 12 months in 1,058 patients (P<0.001). The incidence rate was above 70% in KD aged less than 18 months and more frequent than those of cervical lymphadenopathy. The logistic regression analyses showed that the principal clinical findings including conjunctivitis (P=0.781), red lips/oral mucosa (P=0.963), rash (P=0.510), cervical lymphadenopathy (P=0.363), changes in extremities (P=0.283) and the coronary artery aneurysm (P=0.776) were not associated with the BCG site reaction.
Conclusions: The BCG site reaction could be a useful diagnostic tool independent to principal clinical findings in KD developing in children aged <18 months, who underwent BCG vaccination. Outcome of KD patients was not different between groups with or without the BCG site reaction in both complete KD and incomplete KD.

Keywords: Kawasaki disease; BCG vaccine; Children; Erythema

INTRODUCTION

Kawasaki disease (KD) is an acute febrile illness of unknown etiology that affects predominantly children aged <5 years of age.[1] KD is currently the most common cause of acquired heart disease in children in developed countries.[1] Currently, there is no definitive diagnostic test for KD. A KD diagnosis is based on clinical criteria including ≥5 days of fever and the presence of at least four of the five principal clinical features (oropharyngeal changes, bilateral conjunctival injection without exudates; polymorphous rash, changes of the extremities, and cervical lymphadenopathy).[1]

Author Contributions

Conceptualization: Yu JJ; Data curation: Park SH, Shin EJ, Jun HO; Formal analysis: Park SH, Yu JJ; Investigation: Park SH, You Jh, Kim MJ; Methodology: Park SH, Yu JJ; Project administration: Park SH, Yu JJ; Resources: Yu JJ; Software: Park SH, Yu JJ; Supervision: Yu JJ, Baek JS, Kim YH, Ko JK; Validation: Yu JJ; Visualization: Park SH; Writing - original draft: Park SH; Writing - review & editing: Yu JJ

Redness or crust formation at the Bacille Calmette-Guérin (BCG) inoculation site is reported in about 30–50% of all KD patients.[2,3] However, it is observed in ≥50% of KD patients at 1 to 12 months after inoculation.[2,4] The BCG site reaction is a useful diagnostic finding especially in children with incomplete presentation of illness.[2-5] The BCG site reaction has been regarded as one type of skin rash of KD by some authors.[6] Comprehensive reports investigating the clinical characteristics of KD patients manifesting the BCG site reaction are rare.[7,8]

The purpose of this study was to investigate the significance of the BCG site reaction as a diagnostic clinical finding and an outcome predictor in young children with KD.

MATERIALS AND METHODS

1. Subjects

Among 1,090 patients who were admitted to the Asan Medical Center for management of acute illness between January 2006 and February 2017, 41 transferred patients without data related to BCG site status or principal clinical features and 1 patient without BCG vaccination were excluded. Age-specific incidence of the BCG site reaction was analyzed in those 1,058 patients. Subsequently, patients aged less than 18 months were enrolled as subjects for the analysis of the association between the BCG site reaction and other laboratory and clinical findings. Subjects were divided into two groups according to the presence of the BCG site reaction in complete and incomplete KD separately.

This study was approved by the Institutional Review Board of Asan Medical Center (2018-0370), and the requirement for informed patient consent was waived.

2. Data acquisition

Demographic, clinical, laboratory, and coronary arterial diameter data were obtained via retrospective review of the medical records of subjects. Diagnosis of KD was made according to the American Heart Association criteria.[1] Complete KD was defined as ≥5 days of fever and the presence of ≥4 of the 5 principal clinical features. Incomplete KD was defined by fever ≥5 days, 2 or 3 principal clinical features, and compatible laboratory or echocardiographic findings without other causal explanation for fever. Spontaneous improvement was defined as resolution of fever without intravenous immunoglobulin (IVIG) treatment. Refractory KD was defined as the requirement for 2nd line treatment to control persistent fever at 36 hours after 1st IVIG treatment. The BCG site reaction was defined as any redness or crust formation at BCG inoculation site recorded during admission.[7]

Laboratory data included white blood cells, hemoglobin, platelet count, erythrocyte sedimentation rate, C-reactive protein, sodium, potassium, chloride, albumin, alanine aminotransferase, aspartate aminotransferase (AST), bilirubin, brain natriuretic-peptide, urine analysis.

A coronary artery diameter measured at subacute phase was converted to z score using the regression equation of McCrindle et el.[9] A coronary artery aneurysm was defined as z score of any coronary arterial branch diameter ≥2.5.[1] Pyuria was defined as ≥10 white blood cells per high power field in microscopic exam.

https://doi.org/10.14776/piv.2018.25.e11

PIV PEDIATRIC INFECTION & VACCINE

3. Statistical analysis

All the data were presented as mean±standard deviation or frequency (%) as appropriate. Continuous data between two groups was compared by t-test. χ^2 test was used to compare frequencies between two groups and to analyze the altered rate of incidence of the BCG site reaction according to age. The association between the BCG site reaction and other variables was investigated separately in complete and incomplete KD groups via univariate logistic regression analysis. A multivariate analysis was performed with statistically significant variables in univariate analysis. To avoid collinearity between variables, we used body weight as the representative variable of body size in multivariate analysis. SPSS version 21.0 (IBM Co., Armonk, NY, USA) was used for all statistical analysis. Statistical significance was defined as a *P*-value <0.05.

RESULTS

1. The incidence rate of the BCG site reaction according to age

The proportions of patients with BCG site reaction in the respective age ranges were above 70% in age group under 18 months (**Fig. 1**). The incidence rate of the BCG site reaction was higher in patients in the age group 6–12 months than in the 0–6 months (*P*=0.017), and significantly decreased with increasing age (*P*<0.001) after 12 months. The 416 patients in the age range 0–18 months were enrolled in subsequent analyses.

2. Characteristics of subjects

The subjects included 313 patients with BCG site reaction and 103 patients without BCG site reaction (**Table 1**). Patients with the BCG site reaction had lower body index, fewer cervical lymphadenopathy, fewer changes in extremities and fewer spontaneous improvement. They also had lower hemoglobin level, higher AST, higher potassium level and more pyuria. Incidence of coronary aneurysm and z scores of three major coronary arteries were not different between two groups.

3. Correlation between the BCG site reaction and other variables in the complete KD groups

The univariate analysis of 322 subjects with complete KD showed that patients with the BCG site reaction had lower body index, fewer spontaneous improvement, lower hemoglobin

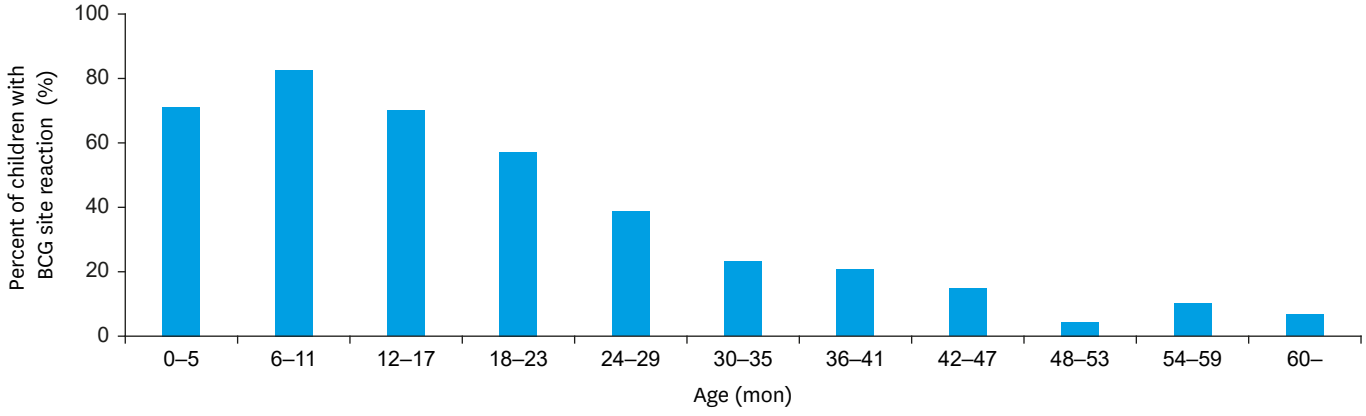

Fig. 1. Age specific proportion of BCG site reaction in 1,058 Kawasaki disease patients. The proportion of the reaction increases until 12 months, then decreases with age.
Abbreviations: BCG, Bacille Calmette-Guérin.

https://doi.org/10.14776/piv.2018.25.e11

Table 1. Characteristics of subjects

Characteristics	BCG site reaction (+) (n=313)	BCG site reaction (–) (n=103)	*P*-value
Age (mon)	8.97±4.65	9.04±5.39	0.901
Male	197 (62.9)	66 (64.1)	0.835
Body weight (kg)	8.97±1.72	10.79±4.22	0.000
Height (cm)	73.40±7.79	80.19±14.57	0.000
Diagnostic criteria			
Conjunctivitis	298 (95.2)	99 (96.1)	1.000
Red lips/oral mucosa	276 (88.2)	93 (90.3)	0.557
Rash	272 (86.9)	90 (87.4)	0.900
Cervical lymphadenopathy	133 (42.5)	56 (54.4)	0.036
Changes in extremities	238 (76.0)	92 (89.3)	0.004
Spontaneous improvement	33 (10.5)	24 (23.3)	0.001
Treatment day (day)	5.75±1.22	5.90±1.30	0.327
Refractory KD	29 (0.09)	17 (0.17)	0.042
Laboratory findings			
WBC ($\times10^3$/uL)	15.1±4.5	14.5±5.9	0.357
Neutrophil (%)	55.5±13.0	56.4±16.6	0.605
Hemoglobin (g/dL)	10.8±1.1	11.1±1.1	0.036
Platelet ($\times10^3$/uL)	355.0±117.7	332.2±95.6	0.080
ESR (mm/hr)	61.4±25.1	59.4±32.7	0.606
Protein (g/dL)	6.4±0.7	6.4±0.7	0.624
Albumin (g/dL)	3.4±0.5	3.4±0.4	0.322
AST (IU/L)	88.9±162.8	57.1±55.4	0.003
ALT (IU/L)	95.1±163.4	71.5±114.9	0.181
Total bilirubin (mg/dL)	0.8±1.0	0.8±0.8	0.771
Sodium (mmol/L)	135.8±2.3	135.9±2.6	0.621
Potassium (mmol/L)	4.5±0.4	4.4±0.5	0.022
Chloride (mmol/L)	102.0±2.6	101.3±3.3	0.058
LD (U/L)	287.7±83.4	303.7±69.3	0.291
C-reactive protein (mg/dL)	8.4±6.0	7.2±6.6	0.096
BNP (pg/mL)	129.7±231.5	120.9±200.5	0.787
Pyuria	129 (42.7)	27 (27.8)	0.009
Coronary artery diameter			
LMCA (mm)	2.11±0.39	2.25±0.49	
Z score	0.16±1.05	0.22±0.99	0.644
LAD (mm)	1.74±0.41	1.78±0.38	
Z score	0.55±1.77	0.35±1.46	0.379
RCA (mm)	1.79±0.44	1.83±0.39	
Z score	0.65±1.43	0.49±1.11	0.366
Coronary artery aneurysm	37 (15.2)	8 (10.4)	0.287

Data are reported as mean±standard deviation or number (%).

Abbreviations: BCG, Bacille Calmette-Guérin; KD, Kawasaki disease; WBC, white blood cell; ESR, erythrocyte sedimentation rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LD, lactate dehydrogenase; BNP, brain natriuretic peptide; LMCA, left main coronary artery; LAD, left anterior descending; RCA, right coronary artery.

Table 2. Logistic regression analysis of the Bacille Calmette-Guérin site reaction in 322 complete Kawasaki disease patients aged less than 18 months

Characteristics	Univariate					Multivariate		
	Reaction (+) (n=231)	Reaction (–) (n=91)	*P*-value	OR	95% CI	*P*-value	OR	95% CI
Body weight (kg)	9.02±1.73	10.80±4.40	0.000	0.763	0.678–0.858	0.001	0.799	0.697–0.916
Height (cm)	73.7±8.1	80.2±14.6	0.000	0.942	0.917–0.967	-	-	-
Spontaneous improvement	16 (6.9)	19 (20.9)	0.001	0.282	0.138–0.577	0.518	-	-
Hemoglobin (g/dL)	10.9±1.1	11.2±1.1	0.017	0.749	0.590–0.950	0.147	-	-
Pyuria	106 (45.8)	25 (27.4)	0.004	2.174	1.273–3.714	0.011	2.124	1.188–3.797

Data are reported as mean±standard deviation or number (%).

Abbreviations: OR, odds ratio; CI, confidence interval.

level and more pyuria (**Table 2**). Other variables including age, principal clinical findings and the z scores of three major coronary arteries were not associated with the BCG site reaction.

https://doi.org/10.14776/piv.2018.25.e11

Table 3. Logistic regression analysis of the Bacille Calmette-Guérin site reaction in 94 incomplete Kawasaki disease patients aged less than 18 months

Characteristics	Univariate					Multivariate		
	Reaction (+) (n=82)	Reaction (–) (n=12)	*P*-value	OR	95% CI	*P*-value	OR	95% CI
Body weight (kg)	8.84±1.70	10.65±2.69	0.005	0.612	0.433–0.865	0.018	0.638	0.440–0.926
Height (cm)	72.5±7.0	80.0±14.7	0.010	0.910	0.848–0.977	-	-	-
Total bilirubin (mg/dL)	0.6±0.5	1.2±1.4	0.026	0.467	0.239–0.913	0.285	-	-

Data are reported as mean±standard deviation.

Abbreviations: OR, odds ratio; CI, confidence interval.

Among the significant variables in the univariate analysis, body weight (odds ratio [OR], 0.799; 95% confidence interval [CI], 0.697–0.916; *P*=0.001) and pyuria (OR, 2.124; 95% CI, 1.188–3.797; *P*=0.011) were still significant variables in the multivariate analysis.

4. Correlation between the BCG site reaction and other variables in the incomplete KD groups

In the univariate analysis of 94 subjects with incomplete KD, patients with the BCG site reaction had lower body index, higher serum total bilirubin level. The body weight (OR, 0.638; 95% CI, 0.440–0.926; *P*=0.018) remained a significant variable in the multivariate analysis (**Table 3**).

DISCUSSION

BCG vaccination for prevention of tuberculosis especially severe infection in children,[10] is included in the national immunization program of South Korea.[11] BCG vaccination has been recommended for newborn infants aged <1 month since 1966,[12] and its coverage was nearly 100%.[11,13] There was only one excluded patient due to lack of vaccination in this study. Therefore, South Korea with the second highest incidence of KD worldwide,[14] should be the most appropriate country to conduct any investigation into the BCG site reaction in KD.

It is well known that incidence of BCG site reaction decreases with age.[2,7,8,15] In this study, the incidence of BCG site reaction peaked at 6 months to 18 months and declined with age. Similar result was found by a study in Japan, where BCG vaccination has been recommended for infants aged <1 year. In a previous study in Japan, BCG site reaction peaked between 6 and 8 months and also decreased with age.[2]

We selected patients aged below 18 months for satisfactory diagnostic sensitivity of investigation into the clinical significance of the BCG site reaction. First, an incidence rate of BCG site reaction was ≥70% in patients aged below 18 months, as shown in **Fig. 1**. Second, BCG site reaction is more frequent than cervical lymphadenopathy in that age group in our study. Third, in a previous study by Uehara et al.,[2] they selected age group 3–20 months with incidence rate ≥70% for analysis of BCG site reaction. An additional purpose of the patient selection was to reduce the strong influence of age on the incidence rate.[2,7,8,15]

Due to the difference between complete KD and incomplete KD, we analyzed the association of the BCG site reaction with the other variables separately for complete and incomplete KD.

The multivariate logistic regression showed that body weight was associated with the BCG site reaction in both complete and incomplete KD groups. The higher body weight was related to a diminished likelihood of the BCG site reaction. First, we interpreted

https://doi.org/10.14776/piv.2018.25.e11

this relationship as a reflection of the time course of weight gain from growth after BCG vaccination. Second, it is well known that immune system of children is still in a course of development and immune system is closely related with the child's nutrition state. For children with higher body weight, the primary immune response to BCG strains may be more complete and faster and may reduce the chance of developing BCG site reaction in infants with KD. We cannot further explain the association of pyuria and the BCG site reaction in complete KD. No association between the BCG site reaction and coronary arterial lesions in this study is compatible with other published reports.[2,3,7,8,15] Therefore, outcome of KD patients was not different between groups with or without the BCG site reaction in both complete KD and incomplete KD.

Currently, BCG site reaction is regarded as skin rash in Korea. But in this study, the BCG site reaction was not associated with any principal clinical findings of diagnostic criteria including skin rash. These findings are compatible with the results of other recent studies in which the frequency of principal clinical findings was not different between groups with or without the BCG site reaction.[7,8] We suggest BCG site reaction as a diagnostic finding independent to skin rash.

Uehara et al.[2] suggested that the BCG site reaction is a useful diagnostic sign in KD among children aged 3 to 20 months in countries with a BCG vaccination program, because the proportion of patients with the reaction was higher than 70% and the cervical lymphadenopathy, which is one of the principal clinical findings, was less than 60% in patients aged ≤24 months. The similar result was also found in our study. In our opinion, the BCG site reaction independent to the principal clinical findings of KD may not regard as a part of skin rash, instead, suggests a possible role as an additional or alternative diagnostic parameter in young children undergoing BCG vaccination.

It is well-known that infants diagnosed with KD frequently show incomplete clinical presentation and longer duration of fever.[16,17] A coronary artery lesion associated with prolonged fever was relatively frequent in infants.[18] The BCG site reaction appears early at 1–4 days after the onset of fever.[2,19] Therefore, we believe that the BCG site reaction represents a useful finding for early diagnosis of KD, especially in young patients undergoing BCG vaccination.

This study has a few limitations. To determine whether the BCG site reaction is diagnostically consistent and compliant with the principal clinical findings, a higher number of patients and a negative control group — children with other febrile illness are needed.

In conclusion, the BCG inoculation site reaction was independent of the principal clinical findings of KD criteria and could be a useful tool for diagnosis of KD in children aged less than 18 months and undergoing BCG vaccination. Outcome of KD patients was not different between groups with or without the BCG site reaction in both complete KD and incomplete KD.

REFERENCES

1. 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

2. Uehara R, Igarashi H, Yashiro M, Nakamura Y, Yanagawa H. Kawasaki disease patients with redness or crust formation at the Bacille Calmette-Guérin inoculation site. Pediatr Infect Dis J 2010;29:430-3.
PUBMED | CROSSREF
3. Rezai MS, Shahmohammadi S. Erythema at BCG inoculation site in Kawasaki disease patients. Mater Sociomed 2014;26:256-60.
PUBMED | CROSSREF
4. Seo JH, Yu JJ, Ko HK, Choi HS, Kim YH, Ko JK. Diagnosis of incomplete Kawasaki disease in infants based on an inflammation at the Bacille Calmette-Guérin inoculation site. Korean Circ J 2012;42:823-9.
PUBMED | CROSSREF
5. Lee SJ, Kim SJ, Kim HS, Sohn S. Clinical characteristics of Kawasaki disease in infants younger than 3 months of age. J Korean Pediatr Soc 2003;46:591-6.
6. Hong CE. Pediatrics. 11th ed. Seoul: Mirae N Co., Ltd, 2016;1276-8.
7. Lai CC, Lee PC, Wang CC, Hwang BT, Meng CC, Tsai MC. Reaction at the Bacillus Calmette--Guérin inoculation site in patients with Kawasaki disease. Pediatr Neonatol 2013;54:43-8.
PUBMED | CROSSREF
8. Garrido-García LM, Castillo-Moguel A, Vázquez-Rivera M, Cravioto P, Fernando G. Reaction of the BCG scar in the acute phase of Kawasaki disease in Mexican children. Pediatr Infect Dis J 2017;36:e237-41.
PUBMED | CROSSREF
9. McCrindle BW, Li JS, Minich LL, Colan SD, Atz AM, Takahashi M, et al. Coronary artery involvement in children with Kawasaki disease: risk factors from analysis of serial normalized measurements. Circulation 2007;116:174-9.
PUBMED | CROSSREF
10. World Health Organization. BCG vaccine. WHO position paper. Wkly Epidemiol Rec 2004;79:27-38.
PUBMED
11. Choe YJ, Yang JJ, Park SK, Choi EH, Lee HJ. Comparative estimation of coverage between national immunization program vaccines and non-NIP vaccines in Korea. J Korean Med Sci 2013;28:1283-8.
PUBMED | CROSSREF
12. Lee HJ. Classification of vaccination and immunization schedule recommended by the Korean Pediatric Society, 2008. J Korean Med Assoc 2008;51:104-9.
CROSSREF
13. Yang HI, Park EY, Kim MY. National immunization survey in South Korea, 2013. Public Health Wkly Rep 2014;7:449-54.
14. Kim GB, Park S, Eun LY, Han JW, Lee SY, Yoon KL, et al. Epidemiology and clinical features of Kawasaki disease in South Korea, 2012–2014. Pediatr Infect Dis J 2017;36:482-5.
PUBMED | CROSSREF
15. Lin MT, Wang JK, Yeh JI, Sun LC, Chen PL, Wu JF, et al. Clinical implication of the C allele of the ITPKC gene SNP rs28493229 in Kawasaki disease: association with disease susceptibility and BCG scar reactivation. Pediatr Infect Dis J 2011;30:148-52.
PUBMED | CROSSREF
16. Manlhiot C, Yeung RS, Clarizia NA, Chahal N, McCrindle BW. Kawasaki disease at the extremes of the age spectrum. Pediatrics 2009;124:e410-5.
PUBMED | CROSSREF
17. Chang FY, Hwang B, Chen SJ, Lee PC, Meng CC, Lu JH. Characteristics of Kawasaki disease in infants younger than six months of age. Pediatr Infect Dis J 2006;25:241-4.
PUBMED | CROSSREF
18. Song D, Yeo Y, Ha K, Jang G, Lee J, Lee K, et al. Risk factors for Kawasaki disease-associated coronary abnormalities differ depending on age. Eur J Pediatr 2009;168:1315-21.
PUBMED | CROSSREF
19. Takayama J, Yanase Y, Kawasaki T. Study of the changes of the site of the BCG inoculation in MCLS. JPN J Pediatr 1982;86:567-72.

PIV PEDIATRIC INFECTION & VACCINE

요약

목적: 가와사키병이 있는 소아에서 진단 및 결과 예측에 있어서 Bacille Calmette-Guérin (BCG) 접종 부위 반응의 임상적 중요성을 알아보고자 하였다.

방법: 2006년 1월부터 2017년 2월까지 가와사키병으로 서울아산병원에 입원한 1,058명의 환자를 대상으로 각 연령대에서 BCG 부위 반응의 발생 빈도를 조사하였다. 이 중 생후 18개월 미만인 416명의 환자를 BCG 부위 반응과 실험실 및 임상 소견들과의 연관성을 분석하기 위한 대상자들로 선정하였다. 분석은 완전형과 불완전형 발현 두 그룹으로 구분하여 수행되었다.

결과: 1,058명의 환자들을 관찰한 결과, BCG 부위 반응의 발생률은 생후 6–12개월(83%) 연령의 환자에게 가장 많았고, 12개월 후 연령이 증가함에 따라 감소했다(P<0.001). BCG 부위 반응은 생후 18개월 미만 환자의 70%이상에서 발생하였고, 경부 림프절 종대보다 빈발했다. 로지스틱 회귀분석결과, 결막염(P=0.781), 입술/구강의 변화 (P=0.963), 발진 (P=0.510), 경부 림프절 종대 (P=0.363), 사지 말단의 변화 (P=0.283) 및 관상 동맥류 (P=0.776)는 BCG 부위 반응과 관련이 없었다.

결론: BCG 부위 반응은 BCG 예방 접종을 받은 18개월 미만 소아에서 가와사키병의 주요 임상 소견과는 독립적으로 유용한 진단 도구가 될 수 있다는 것을 확인하였다. 관상동맥 합병증 결과는 완전 가와사키병 및 불완전 가와사키병 모두에서 BCG 부위 반응이 있거나 없는 그룹간에 차이가 없었다.

https://doi.org/10.14776/piv.2018.25.e11