

# Predicting Factors of Roseola Infantum Infected with Human Herpesvirus 6 from Urinary Tract Infection

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**Purpose:** The aim of this study was to compare the clinical and laboratory features of infants with roseola infantum due to human herpesvirus 6 (HHV6) infection and those with urinary tract infection (UTI).

**Methods:** We retrospectively reviewed the medical records of children who were hospitalized at Cheil General Hospital and Women's Health Care Center, College of Medicine, Dankook University, and diagnosed as having HHV6 infection or UTI.

**Results:** Among the infants admitted between September 2014 and May 2016, 92 (male, 45 and female, 47) were included in the study and divided into a HHV6 infection group (n=50) and a UTI group (n=42). The relative risk of UTI compared with that of HHV6 infection increased with pyuria ( $P<0.001$ ), increased with leukocytosis (mean white blood cell [WBC] count,  $15,048\pm5,756/\text{mm}^3$  vs  $87,916\pm54,056/\text{mm}^3$ ;  $P<0.001$ ), increased with C-reactive protein (CRP) level ( $4.89\pm4.85$  mg/dL vs  $1.04\pm1.76$  mg/dL;  $P<0.001$ ), and younger age ( $6.3\pm3.2$  months vs  $18.3\pm12.6$  months;  $P<0.001$ ). The relative risk of HHV6 infection compared with that of UTI increased with fever duration ( $4.3\pm1.7$  days vs  $2.8\pm1.7$  days;  $P<0.001$ ) and decreased with platelet (PLT) count ( $373\pm94\times10^3/\text{mm}^3$  vs  $229\pm90\times10^3/\text{mm}^3$ ;  $P<0.001$ ). No significant differences were found between the HHV6 groups according to the presence or absence of pyuria.

**Conclusion:** Pyuria, age, fever duration, WBC count, CRP level, and PLT count were the differentiating factors of HHV6 infection from UTI. However, sterile pyuria can occur in children with HHV6 infection. In the presence of pyuria, CRP level and PLT count were the strong predictors of UTI compared with HHV6.

**Key words:** Roseola infantum, Human herpesvirus 6, Urinary tract infection, fever, Pyuria

## Introduction

Roseola infantum, also known as exanthema subitum or sixth disease, is an acute benign febrile exanthem of childhood. It is a clinical syndrome characterized by three to five days of high fever (may exceed  $40^\circ\text{C}$  [ $104^\circ\text{F}$ ]) that resolves abruptly and is followed by development of a rash<sup>1,2</sup>. The disease initially manifests as a sudden-onset high fever, typically lasting 3-5 days<sup>3</sup>. Macular or papular rashes appeared on face, trunk, or both, mostly at the time of subsidence of the fever and other clinical manifestations occurred as follows: mild diarrhea, edematous eyelids, erythematous papules in the pharynx, cough, and mild cervical lymph node swelling<sup>3-6</sup>.

But early in roseola infantum, other clinical symptoms except fever, did not always occurred in all patients. So, differential diagnosis of roseola infantum with urinary tract infection (UTI) is difficult because the initial symptom of fever without other symptom is also suggestive of UTI which is common disease in children<sup>7)</sup>. In such cases, urinalysis is thought to be the best ways for ruling out UTI and avoiding unnecessary antibiotic treatment. But it is often difficult to differentiate both diseases, if there is pyuria in patients with roseola infantum. Because it takes at least 3-4 days to differentiate the two diseases until a characteristic rash occur from the patient or it is proven to grow bacteria in the urine, it is very difficult to differentiate between roseola infantum and UTI. The aim of this study is to compare the clinical and laboratory features of children with roseola infantum caused by human herpesvirus 6 (HHV6) and UTI for early differential diagnosis.

## Materials and methods

A total of 92 children who were admitted to the Cheil General Hospital and Women's Healthcare Center, Dankook University, College of medicine for HHV6 or UTI during September 2014 to May 2016 were enrolled. We reviewed the medical records of 50 infants diagnosed with HHV6 and 42 infants diagnosed with UTI and analyzed retrospectively. This study was approved by the Institutional Review Board and Research Ethics committee of the Cheil General Hospital and Women's Healthcare Center (IRB No.CGH-IRB-2016-51).

Roseola infantum was diagnosed if infants had typical clinical symptoms of the disease, including an initial fever of between 38.9°C and 40.6°C for 3-5 days, restlessness and irritability (but otherwise alert), and mild cervical or, less frequently, occipital lymphadenopathy within 12-24 hours of fever resolution<sup>8)</sup>. The characteristic exanthem of roseola is faint, rose pink in color, and consists of discrete irregular circular or elliptical macules or papules that measure 2-3 mm in diameter and blanch under pressure<sup>9)</sup>. The eruption occurs predominantly on the neck and trunk, though it can spread to the face and extremities<sup>10)</sup>. We confirmed the diagnosis of roseola infantum by detection of HHV6 virus through the polymerase chain reaction.

Urine samples were collected using a urine bag after sterilizing on genital area with hibitan solution (chlorhexidine gluconate solution 0.25 mL/mL). After sterilization, a sterile urine bag was gently attached to the area using adhesive strips and urinalysis was done as soon as possible after voiding. UTI was diagnosed if the urinalysis result is positive, the patient is symptomatic, and there is a single organism cultured with a colony count >100,000<sup>11)</sup>.

Fever was defined as ear (tympanic membrane) temperature above 38°C<sup>12)</sup>.

Pyuria is defined as the presence of 3 or more white cells per high-power field of unspun urine<sup>13)</sup>. Inflammation was indicated by a C-reactive protein concentration (CRP) >0.5 mg/dL.

Age at diagnosis, sex, white blood cell count (WBC), platelet count (PLT), CRP concentration, season of disease onset, duration of fever, and peak degree of fever were compared between infants who had HHV6 infection and UTI, and also between infants who had HHV6 infection with pyuria versus infants who had HHV6 infection without pyuria.

Statistical analysis was performed using SPSS version 20.0 (SPSS, Inc., Chicago, IL, USA) and a *P* value of less than 0.05 was considered as statistically significant. Continuous variables were expressed as mean±standard deviation (SD) and were compared between groups with the Mann-Whitney U-test. Pearson correlation analysis was performed to examine the relationship between two continuous variables and multiple logistic regression analysis was performed to find independent predictive factors.

## Results

Total 97 (male 45, female 47) infants were included: 50 in the HHV6 group and 42 in the UTI group. The demographic and clinical characteristics of infants with HHV6 and infants with UTI are summarized in Table 1. Infants in the HHV6 group were significantly older and had a longer duration of fever than infants in the UTI group (*P*<0.001). And they had a tendency of lower PLT than infants in the UTI group (*P*<0.001). On the other hand, it was evident that infants in the UTI group had pyuria (*P*<0.001), leukocytosis (*P*<0.001) and higher CRP >0.5 mg/dL (*P*<

0.001) compared with the HHV6 group. There were no significant differences in sex and season.

On univariate logistic regression analysis, age, fever duration, laboratory finding such as WBC counts, PLT counts, CRP level and pyuria were significant differentiating predictors ( $P<0.05$ ) of HHV infection from UTI. Multivariate analysis showed that the most strong risk factor of UTI was pyuria. But infants in the HHV6 group can also have pyuria. So when pyuria is exist, increasing WBC ( $P<0.001$ ), decreasing age ( $P=0.003$ ) and increasing CRP ( $P=0.006$ ) were risk factors of UTI. And the risk of HHV6 is increased as PLT is decreased ( $P=0.001$ ).

The demographic and clinical characteristics of infants with HHV6 who did and did not have sterile pyuria are summarized in Table 2. There were no significant differences in age, sex, seasonal incidence, peak body temperature, fever duration, WBC, CRP, or PLT in between-group differences, it is difficult to differentiate HHV6 when pyuria exist.

The demographic and clinical characteristics of infants with HHV6 who have pyuria and UTI are summarized in Table 3. Of the 50 infants with HHV6, 17 (34%) were found to have sterile pyuria. If a patient has high fever and pyuria, age ( $P<0.001$ ), WBC ( $P=0.00$ ), CRP ( $P<0.001$ ), and PLT ( $P<0.001$ ) may be predicting factors of HHV6 from urinary tract infection.

## Discussion

Roseola infantum is the disease that affects a child between six months and two years of age, and begins with a sudden high fever. Generally, until the characteristic rash appears, other symptoms do not appear.

UTI is a common source of fever in pediatric patients, and it's clinical findings are frequently nonspecific, making recognition and diagnosis challenging<sup>14</sup>.

**Table 1. Characteristics of HHV6 or UTI**

	HHV6 n=50 (%)	UTI n=42 (%)	P
Age (months)*	18.3±12.6	6.3±3.2	<0.001
Sex (F:M)	29 (58.0)/21 (42.0)	18 (42.9)/24 (57.1)	0.148
Season (Spring/Summer/Fall/Winter)	19 (45.2)/2 (4.8)/9 (21.4)/12 (28.6)	23 (46.0)/11 (22.0)/11 (22.0)/5 (10.0)	0.028
Peak BT (°C)	39.3±0.6	38.9±0.8	0.005
Fever duration (day)*	4.3±1.7	2.8±1.8	<0.001
WBC (/mm <sup>3</sup> )*	8791±5405	15048±5756	<0.001
PLT (x10 <sup>3</sup> /mm <sup>3</sup> )*	236±107	373±94	<0.001
CRP (mg/dL)*	1.35±2.10	4.89±4.85	<0.001
Pyuria (/HPF)*	0.34±0.47	0.85±0.35	<0.001

Data shows mean±standard deviation (SD).

\*Statistically significant between-group difference.

Abbreviations: BT, body temperature; WBC, white blood cell count; PLT, platelet count; CRP, C-reactive protein concentration; HHV6, roseolar infantum caused by human herpes virus 6; UTI, urinary tract infection; Pyuria, presence of 3 or more white cells per high-power field of unspun urine.

**Table 2. Patient Characteristics in accordance with the Presence of Pyuria in HH6 Infection**

	HHV6 with pyuria n=17 (%)	HHV6 without pyuria n=33 (%)	P
Age (months)	17.1±9.4	18.8±14.0	0.848
Sex (F:M)	10 (58.8)/7 (41.2)	19 (57.6)/14 (42.4)	1.00
Season (Spring/Summer/Fall/Winter)	6 (35.3)/3 (17.6)/5 (29.4)/3 (17.6)	17 (51.5)/8 (24.2)/6 (18.2)/2 (6.1)	0.390
Peak BT (°C)	39.1±0.6	39.5±0.6	0.009
Fever duration (day)	4.0±1.6	4.4±1.8	0.446
WBC (/mm <sup>3</sup> )	9481±6111	8436±5068	0.455
PLT (x10 <sup>3</sup> /mm <sup>3</sup> )	229±90	240±116	0.846
CRP (mg/dL)	1.04±1.76	1.50±2.27	0.416

Data shows mean±standard deviation (SD).

Abbreviations: BT, body temperature; WBC, white blood cell count; PLT, platelet count; CRP, C-reactive protein concentration; HHV6, roseolar infantum caused by human herpes virus 6; UTI, urinary tract infection.

Table 3. Patient Characteristics of HHV6 with Pyuria or UTI

	HHV6 with pyuria n=17	UTI n=42	P
Age (months)*	17.1±9.4	6.3±3.2	<0.001
Sex (F:M)	10 (58.8)/7 (41.2)	18 (42.9)/24 (57.1)	0.410
Season (Spring/Summer/Fall/Winter)	6 (35.3)/3 (17.6)/5 (29.4)/3 (17.6)	23 (46.0)/11 (22.0)/11 (22.0)/5 (10.0)	0.315
Peak BT (°C)	39.1±0.6	38.9±0.8	0.48
Fever duration (days)	4.0±1.6	2.8±1.8	0.19
WBC (/mm <sup>3</sup> )*	9481±3,542	15,048±5,756	0.001
PLT (x10 <sup>3</sup> /mm <sup>3</sup> )*	229±90	373±94	<0.001
CRP (mg/dL)*	1.04±1.76	4.89±4.85	<0.001

Data shows mean±standard deviation (SD).

\*Statistically significant between-group difference.

Abbreviations: BT, body temperature; WBC, white blood cell count; PLT, platelet count; CRP, C-reactive protein concentration; HHV6, roseola infantum caused by human herpes virus 6; UTI, urinary tract infection.

Same as above, infants with roseola infantum and UTI initially present with high fever and without other symptom, it is difficult to differentiate these diseases rapidly. In this study we reviewed the medical records of infants with HHV6 who diagnosed with viral study confirmation and UTI for identifying factors that may predict the differential diagnosis of these conditions. Indeed, we found that pyuria, increased WBC and CRP and younger age were the strongest predictors of UTI as determined by multivariate regression analysis.

We also described a small cohort of infants with HHV6 and pyuria. In our study, if pyuria exist, increased WBC and CRP and younger age were the strongest predictors of UTI and decreased PLT is the strongest predictors of HHV6.

Previously there was a report the describe roseola infantum and sterile pyuria<sup>15)</sup> but the viral testing confirmation for diagnosis of roseola infantum were not done in the study. To our knowledge, this is the first report to confirm the HHV6 infection through the viral study in the patients with roseola infantum combined with pyuria.

We found that a relatively high proportion of infants diagnosed with HHV6 may have pyuria (34%) and can be frequently misdiagnosed as UTI during initial presentation before more obvious clinical symptoms appear. We suppose that sterile pyuria with roseola infantum may be related with viremia of HHV6. In patients with roseola infantum, there were no significant difference of demographic finding in accordance with the presence of pyuria. In 6 patients of HHV6 with pyuria showed positive results in urine culture.

With this study, high WBC count ( $P<0.001$ ) and elevated

CRP levels higher than 0.5 mg/dL ( $P<0.001$ ) can be strong predictors of UTI. And also older age, longer duration of fever, and lower PLT counts suggest HHV6 infection. Actually, PLT was not decreased below the normal range (150K) in all patients with roseola infantum, there was obvious tendency of decreasing PLT in HHV6. Indeed, in the 12 patients (24%) with roseola infantum showed a decrease in PLT below the normal compared to none of UTI patients showed a decrease PLT.

In our study, high proportion of patients with roseola infantum (98.0%) and all patients with UTI were treated with antibiotics. Fever duration after antibiotics treatment make no difference between UTI (1.4±1.2 days) and HHV6 (1.7±1.1 days). Probably, fever was subsided in patients of UTI in accordance with antibiotics treatment. But in patients with roseola infantum, fever was subsided in accordance with the natural progress of viral infection. Early differential diagnosis of roseola infantum and UTI is should help to reduce the use of antibiotics in viral infection.

A limitation of the present study was that the small cohort of study and the use of urine bags for collection of urine samples which can make contamination. Despite of contamination possibility, urine bag is better way for urine collection because of being noninvasive. Further study may be needed with large cohort of HHV6 and roseola infantum with other virus such as HHV7.

## Conclusion

Age, fever duration, WBC, CRP and PLT and urinalysis

may be useful for making a tentative diagnosis when infants present with high fever and are suspected of having HHV6 or UTI.

But, in our study about 34 % cases in HHV6, pyuria was occurred. In that cases in which diagnostic uncertainty exists, urine culture is thought to be the best means of ruling out UTI.

Before urine culture result is coming out, age, CRP and PLT may be useful for preventing unnecessary antibiotics therapy. This is the first paper which compared clinical characteristics of HHV6 which was confirmed by viral testing for HHV-6 versus UTI and suggest PLT as a predictable factor.

## Conflicts of Interest

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

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