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HHV6 involvement in pediatric drug hypersensitivity syndrome

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Abstract

Background—HHV6-positivity in context of drug hypersensitivity syndrome (DHS) may influence disease severity. Systemic corticosteroid treatment of those with DHS, testing positive for HHV6, has been speculated to prolong the duration of disease.

Objectives—This study's objectives are to: (1) Evaluate whether DHS patients with HHV6-positivity develop a more severe illness compared to DHS patients without presumed reactivation in the pediatric population, and (2) Evaluate the response to systemic corticosteroid treatment.

Methods—Retrospective case series of 29 pediatric inpatients treated for DHS and tested for HHV6. HHV6-positive and -negative patients were identified and stratified to groups treated with and without systemic corticosteroids to examine their disease severity on the basis of hospital length-of-stay (LOS), total number of febrile days (T_{feb}), and days until cessation of progression (CTP).

Results—HHV6-positive patients had similar demographic characteristics as HHV6-negative patients, but had significantly longer hospital LOS (11.5 days v 5 days, $p=0.0386$), T_{feb} (12.5 days v 3 days, $p=0.0325$), and CTP (4 days v 2 days, $p=0.0141$). All HHV6-positive patients and most (80%) of the HHV6-negative patients received systemic corticosteroids. Among the HHV6-negative patients, those who received corticosteroids showed significantly shorter CTP than those who did not receive corticosteroids (3 days v 2 days, $p=0.043$). Additionally, there was a trend towards shorter hospital LOS and T_{feb} among HHV6-negative patients who received corticosteroids when compared with those who did not, though these differences were not statistically significant. The most common inciting drugs included trimethoprim-sulfamethoxazole (33%), phenytoin (10%), and amoxicillin (10%).

Conclusions—HHV6-positivity with DHS is associated with a more severe disease course. Treatment with systemic corticosteroids was associated with a non-statistical trend toward reduced

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hospital LOS and febrile days, and a statistically reduced number of days until cessation of progression.

Keywords

Human herpesvirus 6; drug hypersensitivity syndrome; systemic corticosteroids

Introduction

Drug hypersensitivity syndrome (DHS), also known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), represents a drug hypersensitivity phenomenon characterized by a constellation of signs, including a morbiliform rash, facial swelling, conjunctivitis, and is variably associated with transaminitis, eosinophilia (blood and urine), atypical lymphocytosis, and occasionally, late-onset thyroid dysfunction, and cardiomyopathy. Rarely, DHS may be an antecedent to more severe reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis.^{1,2}

A number of drugs have been associated with DHS, the most common being anti-epileptics, antibiotics, antivirals, and allopurinol.³ In addition to Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus 7 (HHV7), human herpesvirus 6 (HHV6) infection has also been associated with DHS.³⁻⁶ Patients with DHS have been reported to have elevated antibody titers to HHV6 or detection of HHV6 on polymerase chain reaction (PCR) studies, although not all patients with DHS manifest an association with HHV6. Some authors have raised concern that HHV6-positivity in context of DHS may influence disease severity in affected patients.⁶⁻⁸ In addition, it has been speculated that systemic corticosteroid treatment of those with DHS and concomitant expression of HHV6 may prolong the drug reaction, although it remains unclear whether the presence of HHV6 is pathogenic or a non-pathogenic marker for disease severity.^{5,6,9} Although systemic corticosteroids have been the mainstay of treatment, their efficacy remains controversial.^{3,5,10-14}

This study evaluated pediatric patients with DHS who have concomitant expression of HHV6 on the basis of increased viral copy number on PCR studies to determine if they present with a different disease course when compared to those with DHS who do not have evidence of HHV6 infection or reactivation. Secondly, this study also evaluated the responses to systemic corticosteroid therapy in these subpopulations.

Materials and methods

Patients and samples

The protocol for this study was reviewed and approved by the Children's Hospital of Philadelphia Institutional Review Board.

Data for this retrospective study were obtained from the Children's Hospital of Philadelphia (CHOP). Between 1996 and 2012, approximately 11,000 pediatric dermatology inpatient consultations were screened for the following inclusion criteria: (i) a documented diagnosis of DHS or DRESS, (ii) an identification of the culprit drug to confirm a drug-associated

etiology, (iii) documentation of HHV6 testing by PCR, and (iv) age $\geq$ 18 years. Patients who had a positive workup for co-infection with viruses other than HHV6, which included EBV, CMV, and HHV7 were specifically excluded.

The PCR methods used to assess HHV6 status remained constant in all patients included in this study. Nucleic acid purification of the whole blood sample was performed using the MagNA Pure System (Roche). The Applied Biosystems thermocycler amplified and quantified the HHV6 U65-U66 gene region by using TaqMan real-time PCR technology. HHV6 positivity was determined by the viral copy number in whole blood as detected by quantitative PCR. HHV6 negativity was determined a quantity of DNA copies that was less than the lower limit of detection of the assay (134 copies/mL). Those who had no documentation of HHV6 testing by quantitative PCR were not included.

Electronic hospital records were reviewed using a standardized data extraction form. Demographic characteristics, RegiSCAR categories, culprit drugs, associated laboratory data, and proxies for disease severity including hospital lengths-of-stay (LOS), total number of febrile days during the course of DHS (T_{feb}), and days until cessation of progression (CTP) were recorded. RegiSCAR categories, as defined by the RegiSCAR Study group, are calculated by a standardized scoring system that combines clinical and laboratory criteria to validate the diagnosis of DHS into “no,” “possible,” “probable,” or “definite” cases.¹⁵ The first available laboratory values were utilized. Number of days until cessation of progression (CTP) was calculated as the difference in days between the onset of symptoms and the earliest time when there was no change in the patient's course of disease and no further decline in laboratory values. Timing of onset of DHS presentation was determined by the number of days between the first day of drug administration and the onset of fever or rash, whichever appeared first. Follow-up visits to the dermatology clinic within 6 weeks of hospitalization were also noted.

Statistical analysis

Data were summarized descriptively. Demographic characteristics and disease severity proxies were compared between HHV6-positive and -negative cases, and between those treated with and without systemic corticosteroids. T-tests were used to compare continuous variables with a normal distribution; Wilcoxon rank-sum tests were used to compare continuous variables with a non-normal distribution; and Fisher's exact tests were used to compare categorical variables. Two-sided tests of statistical significance ($\alpha = 0.05$) were used for all analyses. Data analysis was performed using Stata/IC 11.0 (StataCorp, College Station, TX).

Results

Approximately half of the patients with DHS had HHV6-testing. Six patients, who tested positive for EBV, CMV, or HHV7, and tested negative for HHV6, were excluded. Twenty-nine patients fulfilled the above criteria for inclusion in this study. All patients were managed with immediate drug discontinuation. Four patients had evidence of HHV6 on PCR studies (median viral load: 11,191 copies/mL, range: 2502-354,065 copies/mL), and 25 patients were negative for HHV6. Among those negative for HHV6, 20 patients were treated

with systemic corticosteroids (median total dosage: 5 mg/kg; range: 1-16 mg/kg) and 5 patients were managed with supportive therapy alone. All four patients positive for HHV6 were treated with systemic corticosteroids (median total dosage: 6.5 mg/kg, range: 2-14 mg/kg). Systemic corticosteroids were administered either intravenously or orally.

Patient demographics

Patient demographics in all patients as well as the stratified populations' demographics are outlined in Table 1. The demographic characteristics (gender, age, ethnicity, RegiSCAR category, and drug class) between the subpopulations of HHV6-positive and -negative patients showed no statistical differences (Table 1). Similarly, the demographic characteristics (gender, age, ethnicity, and drug class) between the subpopulations of those treated with and without systemic corticosteroids showed no statistical differences in the HHV6-negative patient population (Table 1). HHV6-negative patients treated with corticosteroids were statistically more likely to have definitive diagnoses compared to those without steroid treatment ($p=0.036$).

Culprit drugs related to DHS cases

In around one-third of the DHS cases, trimethoprim-sulfamethoxazole (TMP-SMZ) was the culprit drug (Table 2). Other major culprit drugs included phenytoin (10%) and amoxicillin (10%). The majority of the culprit drugs were antibiotics ($n=21$). Indications included prophylaxis after dental procedure, acne, or infections, such as urinary tract infections, pharyngitis, sinusitis, otitis media, pyelonephritis, enterocolitis, lyme meningitis, abscesses, and pneumonia.

Internal organ involvement during DHS course

All patients in this series had abnormal liver function tests. Four patients, half of whom were HHV6-positive, had pulmonary involvement, which included pneumonia, atelectasis, and pleural effusion. One HHV6-negative patient during hospitalization had mildly elevated levels of thyroxine, which resolved upon discharge. One HHV6-positive patient showed elevated levels of amylase and lipase, whereas one HHV6-negative patient showed elevated levels of amylase only. One HHV6-negative patient was diagnosed with inflammatory myocarditis. One HHV6-negative patient was hypotensive upon presentation. Most patients ($n=15$) in this study recovered completely with the exception of several patients as noted in the "Miscellaneous Adverse Events" section below.

Timing of onset of DHS presentation and HHV6-positivity

The median number of days between first day of drug administration and onset of symptoms for the total population for whom data were available ($n=28$) was 9 days (IQR: 4.5-14.5). When stratified by HHV6 status, the median number of days between the first day of drug administration and the onset of symptoms in the HHV6-positive population was 16.5 days (IQR: 11.5-24) as compared to 7.5 days (IQR: 3.5-14) for the HHV6-negative population ($p=0.070$ by Wilcoxon rank-sum test). When restricted to definite DHS cases that demonstrated HHV6 positivity, the median delay to onset of presentation was 20 days (range: 10-28).

There was no statistically significant difference in the number of days from rash onset to HHV6 testing between HHV6-positive (6.8 days) and HHV6-negative (5.6 days) patients ($p=0.482$).

HHV6-positivity and DHS severity

HHV6-positive cases had significantly longer hospital lengths-of-stay (LOS), total number of febrile days during the course of DHS (T_{feb}), and days until cessation of progression (CTP), when compared to HHV6-negative cases (Table 1).

Corticosteroid use and DHS cases

Although not statistically significant, 80% of patients who were HHV6-negative received systemic corticosteroids versus 100% of those who were HHV6-positive ($p=0.447$). Since there were no HHV6-positive patients who did not receive systemic corticosteroid treatment, the interaction between HHV6-positivity and impact of systemic corticosteroid treatments could not be directly evaluated. Restricting the analysis to the 25 patients who were negative for HHV6, a non-statistical trend towards shorter LOS and T_{feb} , and a statistically shorter CTP were observed when comparing those treated with to those treated without systemic corticosteroids (Table 1).

Laboratory values

First available reports of laboratory values were compared between HHV6-positive and -negative populations. No statistical differences between HHV6-positive and negative cases were noted with regard to the following parameters: eosinophilia, atypical lymphocytosis, and most measures of liver function (AST, ALT, and alkaline phosphatase). There was a statistically significant difference in GGT values between the 4 HHV6-positive cases with a median value of 390.5 U/L (IQR: 192-892), and the 24 HHV6-negative cases with value of 58.5 U/L (IQR: 23.5-144.5) ($p=0.0356$). In addition, there were no statistically significant differences in laboratory values between patients with and without systemic corticosteroid treatment.

Miscellaneous adverse effects

Several adverse effects attributed to systemic corticosteroid therapy were reported, including recrudescence of DHS secondary to a rapid taper of corticosteroids, steroid-induced acne exacerbation in three patients, atopic dermatitis flare secondary to tapering steroids in one patient, mild neutropenia in one patient treated with corticosteroid, and steroid-induced hyperglycemia and hypertension in another patient. Also noteworthy were several adverse effects in three HHV6-negative patients who did not receive systemic corticosteroids including re-hospitalization one week later due to recurrence of transaminitis (tripling of values) following initial discharge in one patient, abnormal thyroid function values one week later in another patient, and xerosis on the lower extremities and post-inflammatory hyperpigmentation upon follow-up in a third patient. Six patients did not have follow-up visits in our dermatology department.

Discussion

Drugs, immunological defects, as well as infections, such as HHV6, have been implicated in the underlying pathophysiology of drug hypersensitivity syndrome (DHS). This retrospective study was conducted to examine the impact of HHV6-positivity on DHS severity and the effect of corticosteroid therapy on these populations.

Demographics

The incidence of DHS is estimated to vary between 1 case in 1,000 drug exposures to 1 case in 10,000 exposures.¹³ Identifying prognostic factors and determining the appropriate treatment for DHS cases is paramount as the mortality rate has been reported to be as high as 10%.¹³ In this study, no patients died.

The detection of HHV6 infection or reactivation has recently been proposed as a diagnostic marker for DHS. In Cacoub et al. review, 80% of HHV6-tested DHS cases were positive, with the total population's mean age was 40.7 years (range: 0.1-84).³ By contrast, in this pediatric case series, only 13.8% of HHV6-tested DHS cases were positive, with the total population's mean age being 11 years (range: 0.42-18 years), suggesting that HHV6 infection or reactivation might be less likely to occur in the context of pediatric DHS.

Although detection of HHV6-positivity on whole blood samples is less specific than serum or plasma for primary infection, a high viral DNA load in whole blood is predictive of primary infection or reactivation.¹⁶ Positive viral cultures or high levels of HHV6 mRNA from reverse transcriptase-PCR in the absence of titers can distinguish primary infection from reactivation.¹⁷ In this study, primary infection from reactivation could not be differentiated. However, since nearly 100% of children have reportedly been infected with HHV6 by 3 years of age,¹⁷ and all HHV6-positive patients in this study were aged greater than 3 years, it is likely that our patients demonstrating HHV6-positivity had viral reactivation rather than primary infection.

Culprit drug and timing of the development of DHS

The main drugs commonly associated with DHS have been carbamazepine and allopurinol.³ However, in this pediatric study, the major culprit drugs were primarily trimethoprim-sulfamethoxazole (34%), amoxicillin (10%) and phenytoin (10%) (Table 2).

HHV6-positive patients had a non-statistically significant longer delay to the onset of DHS symptoms. It might be speculated that the delay in these cases to the onset of symptoms and signs is related to reactivation of HHV6. It is also interesting to note that the median number of days between the first day of drug administration and the first day of onset of symptoms of fever or rash in this series (n=28) is 9 (IQR: 4.5-14.5), which is similar to the median number of days in the Uhara et al. study of 10.5 (4-16).¹⁰ While several studies have reported the delay in onset of systemic symptoms ranging two to six weeks,^{3,18} the number of days to visceral organ involvement was not noted in this series.

HHV6 - a prognostic factor for severe DHS cases

Several mechanisms regarding the relationship between HHV6 and DHS have been proposed. It has been speculated that culprit drugs may trigger reactivation of the patients' dormant HHV6 that drives selection of CD8+ T-lymphocytes, which subsequently target multiple organ systems.¹⁹ On the contrary, others have suggested that the virus is directly responsible for the cutaneous and visceral manifestations.^{4,18} It has also been hypothesized that the dysfunctional immune response associated with DHS leads to HHV-6 reactivation.¹⁸ The immunomodulatory and cytotoxic effects of HHV6 may prolong the disease course and result in a more severe presentation, warranting the prompt administration of anti-inflammatory treatment.

In concordance with several case series and reports,⁴⁻⁶ HHV6-positive cases exhibited more severe disease on the basis of increased LOS, T_{feb} , and CTP compared to HHV6-negative cases. The universal administration of systemic corticosteroids for HHV6-positive cases could represent greater severity of these patients at the time of presentation.

Systemic corticosteroid impact

The primary initial intervention in DHS cases is the withdrawal of the culprit drug. This study included only patients for whom the culprit drug was identified and withdrawn from administration. In addition, the use of systemic corticosteroids has been commonly employed for the treatment of DHS, although its efficacy has been questioned in several reports.^{3,5,10-14}

In this study, those receiving systemic corticosteroids showed a non-statistical trend toward shorter LOS and T_{feb} and a statistically reduced number of days to CTP. It should be noted that the lack of statistical significance could be due to the study's limited power. It is also possible that there was confounding by indication; specifically, patients with less severe disease were more likely to receive systemic corticosteroids. However, this seems unlikely since systemic steroids would presumably more likely be utilized for patients with more severe disease. It should also be noted that those treated with corticosteroids in the HHV6-negative population tended to have more definite cases than those treated with supportive therapy. This may be a reflection of the treatment bias, in which more definitive cases of DHS were treated with corticosteroids.

In addition, it has been speculated that systemic corticosteroid treatment of those with DHS and concomitant expression of HHV6 may prolong the duration of the adverse drug reaction.^{5,6,9} Since those who were not treated with systemic corticosteroids all tested negative for HHV6, it remains unclear from these cases whether systemic corticosteroids decrease disease severity or prolong the drug reaction in DHS cases with HHV6-positivity.

Internal organ involvement during DHS course

All patients had liver involvement in this series, which may have been used as a diagnostic criterion by the documenting clinicians. This is consistent with reported literature that the liver is most commonly affected organ in DHS.³ Higher GGT values reported in HHV6-positive than HHV6-negative patients may be a reflection of the longer incubation period

observed in HHV6-positive cases as noted previously. Alternatively, one might argue that the virus itself could be responsible for the marked elevation in GGT.^{4,18} Regardless of the etiology, this observation supports the fact that HHV6-positive patients tended to have more serious disease.

Since around 14% of the total study population (and 50% of the HHV6-positive population) had pulmonary complications during hospitalization, it may be advisable to monitor pulmonary symptoms in affected patients.

Study limitations

This retrospective review of all cases of DHS, for which HHV6-testing was performed at a large tertiary children's hospital, was limited by the sample size and number of events within stratified subgroups. All of the patients who demonstrated HHV6-positivity were treated with systemic corticosteroids; therefore, an interaction could not be observed between HHV6-negativity and systemic corticosteroid treatment on the basis of several markers of disease severity.

Selection bias may be introduced by the fact that patients hospitalized at this tertiary care academic center may represent more severe cases than in the general population, thereby limiting the study's external validity. Moreover, this study's population only included those patients with DHS who were screened for HHV6; it is possible that underlying differences in disease severity may have prompted clinicians to likely screen for HHV6-positivity. However, the fact that approximately half of all patients with DHS were tested for HHV6 is likely a result of recent evidence implicating HHV6 in DHS pathogenesis.³ Since the impact of HHV6 on DHS prognosis is not well-established in the pediatric population, there were no standards of care or guidelines for testing at the time of the study.

Conclusions

In DHS cases, HHV6-positivity appears to be associated with a more severe disease course, and a later onset following drug exposure than those without HHV6. HHV6-positive patients have longer hospital LOS, T_{feb}, and CTP than those who were HHV6-negative.

Since all HHV6-positive patients were treated with systemic corticosteroids, the specific role of systemic corticosteroids in this context is unclear. However, treatment with systemic corticosteroids in HHV6-negative cases trends toward better outcomes as documented by improvements in LOS, T_{feb}, and CTP. A larger study may help to further clarify the role of systemic corticosteroids in DHS cases.

We recommend that HHV6-associated pediatric DHS cases should be cautiously monitored for a more severe course and a greater degree of systemic involvement, with attention to the development of pulmonary complications. The utility of HHV6 screening in the context of DHS remains to be more fully elucidated, but it may prove to be a useful prognostic indicator in patients with DHS.

Abbreviations

DHS	Drug Hypersensitivity Syndrome
LOS	Hospital length-of stay
T_{feb}	Total number of febrile days
CTP	Number of days to cessation of progression
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
GGT	Gamma-glutamyl transpeptidase

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- What is known? HHV6 has been associated with a more severe form of drug hypersensitivity syndrome (DHS) in the general adult population. Systemic corticosteroids administration is the mainstay treatment of DHS.
- What does this study add? This study adds a retrospective series to evaluate the factor of HHV6-positivity on DHS progression in pediatric patients. It also evaluates the efficacy of systemic corticosteroids in DHS patients.

Table 1

Patient demographics and proxies of disease severity in the general population and its stratification into subgroups

	All DHS Cases	All DHS Cases (N=29)			HHV6- Patients (N=25)		
	N=29	HHV6- N=25	HHV6+ N=4	P-value	No Steroid N=5	Steroid N=20	P-value
Gender (% Female)	45%	52%	0%	0.103 [^]	40%	55%	0.645 [^]
Mean age in years	11 (range: 0.42-18)	11.2 (range 0.42-18)	6 (range 3-15)	0.153 [*]	9.6 (SD 4.16)	11.6 (SD 5.23)	0.306 [*]
Ethnicity							
White	41%	40%	50%		60%	35%	
Black	38%	36%	50%		0%	45%	
Asian/Pacific Islander	10%	12%	0%		40%	5%	
Hispanic	10%	12%	0%	1.000 [*]	0%	15%	0.054 [*]
RegiSCAR Category							
Possible	7%	8%	0%		40%	0%	
Probable	62%	68%	25%		60%	70%	
Definite	31%	24%	75%	0.145 [*]	0%	30%	0.036 [*]
Drug Class							
Anti-epileptic	31%	28%	50%		20%	30%	
Antibiotic	69%	72%	50%	0.568 [*]	80%	70%	1.000 [*]
Received Systemic Steroids (%)	83%	80%	100%	1.000 ^{**}			
Length of stay in days[*]	5 (range: 1-18)	5 (IQR 3-8)	11.5 (IQR 6.5-16.5)	0.0386 ^{**}	6 (IQR 5-8)	4 (IQR 2.5-7.5)	0.101 ^{**}
Febrile days[*]	4 (range: 0-17)	3 (IQR 2-5)	12.5 (IQR 6-16.5)	0.0325 ^{**}	5 (IQR 3-6)	3 (IQR 2-5)	0.303 ^{**}
Days until cessation of progression[*]	3 (range: 1-16)	2 (IQR 2-3)	4 (IQR 3.5-10)	0.0141 ^{**}	3 (IQR 3-4)	2 (IQR 1.5-3)	0.043 ^{**}

Notes: SD Standard Deviation, IQR interquartile range, HHV6+ HHV6-positive, HHV6- HHV6-negative

^{*} Fisher's exact test

[^] t-test

^{**} Wilcoxon rank-sum test

Table 2

Culprit Drugs Involved and Timing of the Development of DHS

Culprit Drug Involved in DHS	# of DHS Cases related to the Drug	Mean number of days between first day of drug administration and onset of symptoms (Range)
Trimethoprim-sulfamethoxazole	10	12.1 (3-36)
Phenytoin	3	17.3 (10-28)
Amoxicillin	3	8 (5-13)
Cephalosporins	2	6 (4-8)
Lamotrigine	2	3 (3-3)
Minocycline	2	14 (14-14)
Macrolides	2	2.5 (2-3)
Oxcarbazepine	2	22.5 (20-25)
Carbamazepine	1	15
Clindamycin	1	6
Zonisamide	1	NR

Notes: NR Not recorded