

Incidence of Antibiotic-Related Rash in Children with Epstein-Barr Virus Infection and Evaluation of the Frequency of Confirmed Antibiotic Hypersensitivity

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Keywords

Allergy · Antibiotics · Drug hypersensitivity · Epstein-Barr virus · Rash

Abstract

Background: The incidence of rash after aminopenicillin treatment in children with Epstein-Barr Virus (EBV) infection was reported to be 80–100%. A few recent studies suggested that the incidence may be much lower during EBV infection. There are no clear data on the incidence of true drug hypersensitivity among these patients. The aim of this study is to determine the incidence of rash and antibiotic allergy after antibiotic treatment in children with EBV infection. **Methods:** Drug hypersensitivity was investigated in antibiotic-treated patients with a positive EBV IgM who developed a rash between 2013 and 2016. **Results:** During the study period, 221 children were diagnosed with EBV infection, and 120 (54.3%) patients were treated with antibiotics during disease. Rash developed in 41 (41/221, 18.6%) patients, and 20 of them (total 120; 16.6%) were treated with antibiotics (most frequently aminopenicillins: 72.5%), and 21 of them (total 101, 20.8%) were not treated with antibiot-

ics ($p = 0.43$). For 10 of the 20 antibiotic-treated patients with a rash, parents did not consent to an allergy workup. Three of the 10 patients who were tested for drug allergy were proven to have amoxicillin-clavulanate hypersensitivity (30%). Five of the patients without workup reacted after reuse of the suspected drug for infection treatment. **Conclusion:** In this study, the incidence of drug hypersensitivity was much lower than previously reported. Some of the reactions that occur during infectious mononucleosis are transient, and some are true drug hypersensitivity reactions. Thus, these patients should be evaluated with allergy tests before these drugs are used again after EBV infection.

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Introduction

Infectious mononucleosis (IM) is a typical, symptomatic primary Epstein-Barr virus (EBV) infection. Primary infection usually occurs in children, adolescents, and

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young people. It is characterized by fever, exudative or membranous pharyngitis, generalized lymphadenopathy, and splenomegaly. Eruptions, which are usually erythematous, macular, and papular or morbilliform and involve the trunk and extremities, may appear during the first few days and last 1–6 days. It may be difficult to distinguish IM from drug allergy [1, 2].

A similar rash was reported following antibiotics, especially ampicillin during EBV infection. In previous studies, 80–100% of EBV-infected patients who receive aminopenicillins are reported to develop a rash [3–5]. “Ampicillin rash” was first reported in the 1960s as a maculopapular rash following ampicillin treatment during IM [4, 5]. Later, this rash was reported with other antibiotics, such as other penicillins, amoxicillin, tetracyclines, cephalosporins, and piperacillin-tazobactam [3, 5–10]. Recent studies suggest that its true incidence may be much lower [10]. The pathogenesis of this reaction is unknown. The rash is thought to be caused by decreased tolerance and/or enhanced immune responses to certain drugs or its metabolites during EBV infection. Generally, the rash is related to the disease, and it has been reported that the reaction will not recur after infection. However, there are reports revealing real drug hypersensitivity causing a rash during EBV infection [11–13].

The aim of this study is to determine the incidence of rash and antibiotic hypersensitivity in antibiotic-treated children with EBV infection. Disease-associated rash or specific sensitization to the drug will be evaluated by allergy workup.

Patients and Methods

The study was conducted in the Ankara Children’s Hematology Oncology Training and Research Hospital. Patients with a positive EBV IgM between 2013 and 2016 were followed and evaluated. Our Ethics Committee approved the study, and written informed consent was obtained from all patients and/or their parents.

Study Group

Children aged 0–18 years with a diagnosis of IM and positive serology for IgM viral capsid antigens were included. Clinical and demographic characteristics, including age, gender, and history of allergic disease/chronic disease, symptoms, physical examination, antibiotic treatment, and laboratory parameters were recorded. Whether children developed a rash and had antibiotic treatment during the disease was also recorded. If the patient had both rash and antibiotic treatment, the time interval between drug intake and reaction, and duration of treatment was determined. These patients were evaluated with oral drug provocation tests at least 6 weeks after clinical resolution of the disease.

Allergy Workup

The initial drug allergy workup started with the standardized ENDA (European Network for Drug Allergy) questionnaire on drug allergy [14]. Reactions occurring within the 1st h were labeled as “immediate reactions” and those occurring after the 1st h as “nonimmediate reactions.” Skin tests and/or oral provocation tests with the suspected drug were performed. If patients had immediate reactions, the skin was tested with a drug provocation test. If patients had nonimmediate nonsevere cutaneous drug reactions, direct provocation tests were performed. Antihistamine medications and other drugs that could affect drug provocation tests were stopped 1 week before testing.

Drug Provocation Tests

Drug provocation tests were conducted in participants for whom other investigations were inconclusive and who had no contraindications to the provocation test. ENDA guidelines for provocation tests were carefully followed [15]. A provocation test involved administering the suspected drug at divided doses every 30 min, until a cumulative dose close to the age/weight-adjusted daily dose of the drug is achieved. The provocation was given in a maximum of 5 doses. The test was discontinued in the event of any adverse drug reaction. An open drug provocation was performed by a physician with full resuscitation backup.

The drug provocation test was considered positive if any objective symptoms or signs were documented, and negative if no sign of drug hypersensitivity was noted following administration of the usual daily dose. After the last dose, the patient was kept under surveillance for at least 2 h in the clinic. Patients were told to continue to use the drug in 2 divided doses for 5 days at home. Parents were instructed to come to the hospital whenever any reaction occurred. They could also reach us by phone in case of any reaction. Written information including the list of forbidden and alternative antibiotics was given to the patients.

Statistical Analysis

Statistical analyses were performed using the SPSS-15 statistical software package (SPSS, Inc., Chicago, IL, USA) for Windows. Numbers and percentages are reported for discrete variables and means and standard deviations for continuous variables. Values are presented as means and standard deviations for data demonstrating a normal distribution and as medians and interquartile ranges (IQR) for data not demonstrating a normal distribution. The χ^2 test was performed to compare nonparametric data, the Mann-Whitney test for nonnormally distributed data, and the independent t test for normally distributed continuous data. A value of $p < 0.05$ was considered statistically significant.

Results

During the study period, EBV infection with positive IgM against viral capsid antigens was diagnosed in 221 children. The mean patient age was 6.4 ± 4.5 years (median 5.5, IQR 2.8–8.9); 142 (64.3%) were male. Twelve patients (5.4%) had allergic disease.

Table 1. Characteristics of the patients (*n*) who used antibiotics during EBV infection

	Patients		Oral provocation test			
	antibiotic treatment	developing rash with antibiotics	positive	negative	could not be performed	could not be performed but rash was reported after suspected drug reuse after infection
<i>Males</i>	81 (67.5%)	14 (70%)	3 (100%)	5 (71.4%)	6 (60%)	4 (80%)
<i>Drugs</i>						
Penicillins	99	10				
Amoxicillin-clavulanate	80	10	3	3	4	4
Ampicillin-sulbactam	7	–	–	–	–	–
Penicillin	11	–	–	–	–	–
Piperacillin-tazobactam	1	–	–	–	–	–
Cephalosporins	16	5				
Cefuroxime	4	2	–	–	2	–
Ceftriaxone	4	1	–	–	1	–
Cefdinir	2	1	–	1	–	–
Cefixime	2	–	–	–	–	–
Cefaclor	1	–	–	–	–	–
Cefepime	1	–	–	–	–	–
Cefotaxime	1	1	–	–	1	–
Cefprozil	1	1	–	–	1	1
Macrolides	4	3				
Clarithromycin	4	3	–	3	–	–
Other						
Clindamycin	1	1	–	–	1	–
Total	120	20	3	7	10	5
Patient age (median), years	5.33	2.69	3.77	1.57	4.21	2.48

Patients Who Developed a Rash

Rash developed in 41 (18.6%) patients during EBV infections. Their mean age was 4.6 ± 3.7 years, and 29 (70.7%) of them were male. There were no statistically significant differences in the characteristics (age, gender, and frequency of comorbid allergic disease: $p = 0.696$, 0.920 , and 0.582 , respectively) between the patients who developed and did not develop a rash. Twenty of the 120 patients treated with antibiotics and 21 of the 101 patients not treated with antibiotics (20.8%) developed a rash (16.6%) ($p = 0.43$).

Patients Treated with Antibiotics

One hundred twenty patients (54.3%) were treated with antibiotics during the disease. Penicillins were the most common antibiotics (n : 99, 82.5%) used, followed by cephalosporins (n : 16, 13.3%), clarithromycin (n : 4), and clindamycin (n : 1) (Table 1). Twenty of them had a rash, which developed at least 1 h after using antibiotics; all were maculopapular. The time of the appearance of the rashes was 4.4 ± 2.3 days (median: 5, range: 1–9) after the

onset of drug therapy, and 1–24 h (median: 8) after the last dose. Eighty-seven patients (72.5%) were treated with aminopenicillins, and 10 of these patients (11.5%) developed a rash.

Median age of the patients who developed a rash during antibiotic use (n : 20) was 2.69 years (IQR: 1.5–7.3), and median age of the patients who did not develop a rash despite antibiotic use (n : 100) was 5.84 years (IQR: 3.1–9.3) ($p = 0.02$). The other patient characteristics (gender and frequency of comorbid allergic disease) were not significantly different between patients with and without rash during antibiotic use ($p > 0.05$).

Workup of Suspected Drug Allergy

Workups of suspected drug allergy were performed on 10 patients (50%) who developed a rash during antibiotic use. Three of them were proven to have amoxicillin-clavulanate hypersensitivity (30%). The characteristics of the patients with proven drug hypersensitivity are shown in Table 2. Hypersensitivity to the suspected drug (amoxicillin-clavulanate in 3, clarithromycin in 3, and cefdinir

Table 2. Characteristics of the patients with positive provocation tests

Age/ gender	Culprit drug	History of maculopapular eruption	Time interval between reaction and provocation	Provocation test result (maculopapular eruption)
2.90 y/M	Amoxicillin-clavulanate	4th day 8 h after the last dose	2.5 months	4th day 6 h after the last dose
3.78 y/M	Amoxicillin-clavulanate	4th day 6 h after the last dose	2 months	4th day 1 h after the last dose
4.68 y/M	Amoxicillin-clavulanate	5th day 10 h after the last dose	1.5 months	4th day 12 h after the last dose

M, male; y, years.

in 1 patient) was not confirmed in the remaining 7 patients (Table 1).

The other 10 patients with a rash who used antibiotics during EBV infection could not be tested because their families did not consent to the allergy workup with the suspected drugs. Five of them (4 treated with amoxicillin-clavulanate and 1 with cefprozil) experienced a rash when they used the suspected drug after EBV infection. Another patient who reacted to ceftriaxone during IM was reported to use penicillin and cefpodoxime (a cephalosporin that has the same side chain as ceftriaxone) safely without any reaction after EBV infection. Another 4 patients (2 on cefuroxime, 1 on cefotaxime, and 1 on clindamycin) did not reuse the suspected drugs after EBV infection.

Discussion

In our study, we found that the incidence of rash is 16.6% after antibiotic treatment in children during EBV infection. The incidence of rash was not more frequent between patients with or without antibiotic treatment. Ten patients with a rash while using antibiotics could be evaluated with allergy workup, and 3 of them were proven to have drug hypersensitivity.

Antibiotics are frequently used during EBV infection because of misdiagnosis and are mostly unnecessary. In a recent study by Hocqueloux et al. [16], it was reported that 65% of children and 52% of adults used antibiotics during IM. In another study in children, antibiotics were administered to 63.3% of the patients [10]. In our study, 54.3% of the patients were treated with antibiotics during IM.

The incidence of rash during IM without drug intake is reported between 9 and 23.1% [3, 4, 10]. The cutaneous rash of IM is occasionally erythematous/maculopapular, and it can last up to 1 week. The rash may be morbilliform, urticarial, vesicular, or purpuric. Rash is reported

to be more frequent in the group using antibiotics during infection. Cutaneous rash may develop in 15.3–69% of patients on antibiotics during infection [3, 17]. It usually develops after 7–10 days of treatment. In a recent study including children, the incidence of rash was higher with antibiotic use (32.9%) than without (23.1%), but the difference was not significant [10]. In our study, skin rashes occurred in 16.6% of patients with antibiotic treatment and 20.7% of patients without ($p > 0.05$).

Ampicillin was the first drug related to rash during EBV infection. The incidence reported was 70–100% [4, 5]. In 1967, increased incidence rates of skin rashes were noted in IM patients given ampicillin by Patel [4] and Pullen et al. [5]. Patel et al. [4] reported that all patients treated with ampicillin (100%) developed a skin rash. In a study by Chovel-Sella et al. [10], rash occurred with amoxicillin in 29.5% and with amoxicillin-clavulanate in 15.5% of patients. In our study, 12.5% of the patients who used amoxicillin-clavulanate and none of the patients using ampicillin-sulbactam developed a rash. This difference between older and newer studies may be caused by the change in antibiotic use with time. Patients were usually treated with amoxicillin, sulbactam-ampicillin, and amoxicillin-clavulanate in recent studies. None of our patients was on ampicillin or amoxicillin monotherapy; instead, they were given combinations including sulbactam and clavulanate. The differences in these compounds may have resulted different effects.

Skin rashes were described with the use of antibiotics other than aminopenicillins, e.g., other penicillins, tetracyclines, cephalosporins, and piperacillin-tazobactam [3, 5–8]. Patel et al. [4] reported that 14% who received penicillin G, cloxacillin, or tetracycline had a rash during EBV infection. In our study, there were cases who developed rash using cephalosporins, macrolides, and clindamycin.

Studies could not define risk factors for the development of rash in patients using antibiotics during EBV in-

fection. Gender and frequency of comorbid allergic disease were not different in our study groups. However, among children who used antibiotics, patients with a rash were younger than their peers. In contrast, Chovel-Sella et al. [10] could not find a significant difference in terms of age between antibiotic users with or without rash, and other studies did not provide data on the subject. Whether age is a risk factor for rash development in antibiotic-treated IM patients needs to be investigated in larger series.

In the past, in general, it was believed that the morbilliform skin rash following antibiotic treatment in IM patients is a transient reaction and not a real allergic reaction. Subsequently, however, cases of true drug hypersensitivity have been reported. Nazareth et al. [18] performed provocation tests with ampicillin in 20 IM patients who developed a rash on ampicillin and reported that 2 of them had a rash during the provocation test. In a study by Renn et al. [12], 3 patients on aminopenicillin for EBV infection developed a rash, and 2 of them had a positive intradermal test: 1 had a positive patch test, and all 3 patients had a positive LTT (lymphocyte transformation test). In a recent report including 10 young adults, 1 of the 10 patients had a positive LTT, and 4 of 6 patients had a positive intradermal test [13]. Jappe et al. [11] evaluated 8 patients with positive EBV serology and rash with antibiotics and reported that 5 patients had a positive patch test; 2 of them had a positive patch test for penicillin, and 1 had a late positive skin prick test for the suspected drug. Four of these patients had a provocation test, and 1 had a positive reaction. In our recent study, direct oral provocation tests in patients with no immediate mild cutaneous reaction were safe, and thus skin tests were not performed in our patients [19]. Ten of the 20 patients underwent provocation tests, and 3 of them (30%) reacted positive. Five of the 10 patients who could not be tested reported a rash after reuse of the suspected drug following recovery from EBV infection. Thus, a total of 8 of the 20 patients (40%) had a reaction after antibiotic reuse in spite of recovery from EBV infection. In our previous study, 4 of 119 patients (3.4%) with a nonimmediate rash after β -lactam antibiotic use had true drug hypersensitivity, a much lower frequency than in these children with EBV infection [19]. These data suggest that true antibiotic hypersensitivity is not as rare as believed among patients with a rash during antibiotic treatment for EBV infection. Patients should be evaluated by allergy tests to confirm whether the reaction is a real hypersensitivity reaction or a transient rash due to the presence of infection.

The pathogenesis of rash during EBV infection treated with antibiotics is not well known. In an earlier study by

Webster and Thompson [20], a dose-dependent widespread ampicillin polymer-mediated lymphocyte stimulation resulted in skin eruptions with altered cell function in IM patients. McKenzie et al. [21] detected elevated antibody-like activity against ampicillin and suggested circulating ampicillin-antibody complexes resulted in disseminated reaction of the small blood vessels. Currently, it is generally accepted that viral infections enhance the risk of developing drug allergy [22]. Drug-induced herpes virus 6, EBV, and cytomegalovirus reactivation with eosinophilia and systemic symptoms and impaired drug detoxication mechanisms are known to induce drug hypersensitivity reactions, which are more likely to develop in patients with human immunodeficiency virus infection [3]. However, the underlying mechanisms are still not elucidated. For EBV-related drug-induced reactions, it is suggested that EBV infection may affect the immune system and decrease tolerance and/or enhance immune reactions to drugs. This may result in a change in the antigenic expression of the drug and its metabolites or may alter immune regulation [11, 12]. A transient decrease in tolerance during infection may be responsible for the transient rash in antibiotic-treated patients who do not experience a reaction following reuse. For patients who develop true drug hypersensitivity, viral infections may be coactivating factors for drug-responsive T cells which could undergo apoptosis without the acute viral infection. Molecular resemblance of the drug to viral molecules and high affinity of β -lactams for viral proteins are also blamed. Suppression of drug detoxification during infection may also play a role [3].

Consequently, the frequency of rash following antibiotic treatment for EBV infection is lower than previously reported. Some of the reactions that occur during IM are transient, whereas others indicate true drug hypersensitivity. Thus, these patients should be evaluated with allergy tests before these drugs are used again after the infection has subsided. Unnecessary use of antibiotics during EBV infection should be avoided in order to decrease adverse reactions.

Disclosure Statement

The authors have no conflicts of interest to declare.

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