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Evaluation of risk factors for recurrence of cutaneous adverse reactions due to anti-seizure medications in children: A retrospective study

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Drug Eruptions; Rash; Antiepileptic Drug; Epilepsy; Carbamazepine

Abstract

Background: Cutaneous adverse reactions (CARs) are one of the most important reasons for anti-seizure medication (ASM) discontinuation in epilepsy. However, such discontinuations can cause an increase in seizures. This study investigates the risk factors for ASM-related rash recurrence in children.

Methods: This retrospective case-control study consisted of the patient group with a single rash due to ASMs (group 1), the patient group with rash recurrence (group 2), and the control group. While the demographic and clinical features of group 1 and the control group were compared in terms of a single rash, group 1 and group 2 were compared for rash recurrence.

Results: Group 1, group 2, and control group consisted of 112, 33, and 166 patients, respectively. Female gender was a risk factor for a single rash (P < 0.001) but not for recurrence (P = 0.439). Presence of atopic disease [odds ratio (OR): 9.5, 95% confidence interval (CI): 3.8-23.1, P < 0.001], family history of drug allergy (OR: 26.3, 95% CI: 9.6-72.1, P < 0.001), and polytherapy (OR: 23.5, 95% CI: 8.7-62.9, P < 0.001) were risk factors for rash recurrence. Aromatic nature of both the ASMs associated with the first rash (OR: 14.4, 95% CI: 3.2-63.2, P < 0.001) and rash recurrence (OR: 11.3, 95% CI: 4.6-27.5, P < 0.001) were determined as risk factors separately.

Conclusion: Careful use of aromatic drugs may prevent recurrence of ASM-related CAR in children, particularly in cases of personal history of allergic disease and family history of drug allergy.

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Introduction

Epilepsy is one of the substantial neurologic problems affecting almost fifty million people worldwide. An estimated 10.5 million children under the age of 15 suffer from epilepsy, accounting for about 20% of the global burden.[1] Most patients can be successfully treated with anti-seizure medications (ASMs) as mono or polytherapy. However, even accurate recognition of seizure type and epileptic syndromes, selection of the most appropriate ASMs, and careful titration of drug dosage are not enough to vouch for the safety of these particular drugs. In fact, ASMs are noteworthy triggers of cutaneous adverse reactions (CARs), accounting for up to 20% of all CAR hospital stays.[2] Although CARs often present a mild clinical demonstration such as maculopapular eruptions, severe CARs are potentially life-threatening, of which the two most common are Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS).[3]

Although immediate discontinuation of the drug is key in case of CAR, particularly severe and life-threatening forms,[4] such discontinuation can lead to seizure relapse and status epilepticus, bringing forth a considerable amount of concern for the clinician. Determining a replacement ASM meeting both of the indispensable criteria such as suitability for the seizure type of patient and being able to be rapidly titrated to an effective and safe blood level is quite difficult. Patients who have previously demonstrated ASM-related CAR but for whom ASM treatment is unavoidable will continue to be more challenging for the clinician because of the higher risk of cross-reactivity meaning recurrence with a new ASM.[5] Most studies of cross-reactivity have been conducted with cohorts of adult patients, leading to limited information on risk factors for this particular issue in the pediatric age group. This study aims to contribute to this growing area of research by exploring demographic and clinical characteristics of pediatric patients with ASM-related CAR with a focus on the risk factors of second rash, which can be guiding for physicians in choosing a second drug.

Materials and Methods

The current retrospective case-control study was conducted on patients of both sexes with CAR while using ASM, aged 0-18 years, admitted to the pediatric neurology department of Dokuz Eylul University Faculty of Medicine between 2012-2022. Age, gender, history of atopic diseases, and family history of drug eruption were noted. Patients with allergic rashes presenting up to eight weeks after initiation or dose increase of ASM were included in the case group. Other possible etiologies of rash in patients other than ASM were carefully dissected and excluded from the study with detailed anamnesis, accompanying physical examination findings, extensive viral and bacterial serological examinations, and other necessary examinations on a case-by-case basis. Atopic dermatitis, allergic rhinitis, asthma, and food allergy were accepted as atopic diseases. Diagnosis of SJS and TEN was established if patients met the probable or very probable ALDEN criteria.[6]

Epidermal necrolysis affecting < 10%, 10%-30%, and > 30% of the total body surface area was defined as SJS, SJS/TEN overlap, and TEN, respectively. Patients who met the probable or definite Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) criteria were diagnosed with DRESS.[7] The case group was further divided into two groups as group 1 and group 2. Group 1 included patients without rash recurrence with a second ASM, while patients with rash recurrence were collected in group 2. The control group consisted of patients with epilepsy of the same age group who had previously used the same ASM without CAR for at least two years. ASMs associated with CAR in both groups 1 and 2 were evaluated in terms of the biochemical properties, duration of use, presence of combination therapy, and immediate reaction (rash in the first hour of drug initiation). Risk factors for a single CAR were determined by comparing the control group, and cross-reactivity risk factors were determined by comparing the group with a single CAR using the statistical methods described below.

The present study was approved by the local ethics committee (number of approval: 2022/29-26). All statistical analyses were conducted using SPSS (version 20, IBM Corporation, Armonk, NY, USA). The variables were investigated using visual (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov test) to determine whether they were normally distributed. While continuous variables were expressed as mean ± standard deviation (SD) and median with an interquartile range (IQR), categorical variables were expressed as a number and percentage. The Mann-Whitney U-test and Kruskal-Wallis H test were used to evaluate continuous variables and the chi-square

and Fisher's exact tests were used to evaluate differences in categorical variables. Relationships between the variables were examined by calculating Pearson's and Spearman's correlation coefficients. Analysis of variance (ANOVA) and the Friedman test were applied for repeated measurements and Durbin-Conover test was used for post-hoc analysis of significant results. A P-value < 0.05 was established as the threshold for determining statistical significance. After identification of statistically significant factors, odds ratios (ORs) and 95% confidence interval (CI) were calculated with logistic regression analysis to estimate the independent risk of each factor for the development of CAR recurrence.

Results

The number of evaluated patients with an ASM-related CAR was 166, of whom five and four were excluded from the study due to insufficient archive data and lack of follow-up, respectively. Twelve of the remaining patients were further excluded, since a second ASM was not initiated after the first ASM-related CAR. Of the 145 patients enrolled as case group, 66.2% (n = 96) were female. The median (IQR) age was 71 (25-96) months. The patients in the case group were evaluated in two groups according to the recurrence of rash with a second ASM, group 1 (without rash recurrence, n = 112) and group 2 (with rash recurrence, n = 33). The median (IQR) ages of the patients in group 1 and group 2 were 60 (27-100) and 84 (13-96) months, respectively. The control group included 166 patients with a median age of 70 months (IQR: 26-98). The female gender, unlike all other demographic and clinical characteristics, was significantly more common in patients with a single rash (n = 76, 68%) compared to the control group (n = 40, 24%) (P < 0.001) (Table 1). However, female gender did not differ significantly between group 1 (n = 76, 68%) and group 2 (n = 20, 61%) (P = 0.439) (Table 2). While the etiology of epilepsy did not differ significantly for a single rash episode, genetic etiologies were significantly more common in group 2 with a rate of 45% (n = 15) (P = 0.005). Atopic diseases were significantly more common in group 2 (P < 0.001), increasing the risk of a second ASM-related CAR 9.5 times (OR: 9.5, 95% CI: 3.8-23.1). Family history of drug allergy was present in 8% (n = 9) and 70% (n = 23) of the patients in groups 1 and 2, respectively (P < 0.001), indicating a 26.3-fold increased risk of second rash (OR: 26.3, 95% CI: 9.6-72.1). Rash recurrence was statistically high in patients with multiple ASM (69.7% vs. 8.9%, P < 0.001, OR: 23.5, 95% CI: 8.7-62.9).

Table 1. Demographic and clinical features of group 1 and control group

Variable	Group 1** (n = 112)	Control group (n = 166)	P*
Age (month) [median (IQR)]	60 (27-100)	70 (26-98)	> 0.999
Age group [n (%)]			
Infant	7 (6.2)	16 (9.6)	0.600
Toddler	12 (11.0)	15 (9.0)	
Preschool age	38 (34.0)	49 (30.0)	
School age	39 (35.0)	67 (40.0)	
Adolescent	16 (14.0)	19 (11.0)	
Female gender [n (%)]	76 (68.0)	40 (24.0)	< 0.001
Epilepsy etiology [n (%)]			
Unknown	50 (45.0)	68 (41.0)	0.800
Infectious	3 (2.7)	4 (2.4)	
Genetic	18 (16.0)	38 (23.0)	
Immune	2 (1.8)	3 (1.8)	
Metabolic	16 (14.0)	18 (11.0)	
Structural	23 (21.0)	35 (21.0)	
Secondary-progressive MS	52 (17.5)		
Atopic diseases [n (%)]	14 (12.0)	10 (6.0)	0.059
Family history of drug allergy [n (%)]	9 (8.0)	11 (6.6)	0.700
The route of administration [n (%)]			0.200
Intravenous	12 (11.0)	7 (4.2)	
Per oral	100 (89.0)	159 (96.0)	
Biochemical characteristics [n (%)]			0.120
Aromatic	58 (52.0)	91 (55.0)	
Nonaromatic	54 (48.0)	75 (45.0)	

*Mann-Whitney U test, Fisher's exact test, Pearson's chi-squared test; **Group 1 includes the patients with only one history of rash.
IQR: Interquartile range

Table 2. Risk factors for a second rash due to anti-seizure medications (ASMs)

Variable	Group 1** (n = 112)	Group 2 (n = 166)	P*
Age (month) [median (IQR)]	60 (27-100)	84 (13-96)	0.900
Age group [n (%)]			
Infant	7 (6.2)	7 (21.0)	< 0.001
Toddler	12 (11.0)	3 (9.1)	
Preschool age	38 (34.0)	0 (0)	
School age	39 (35.0)	23 (70.0)	
Adolescent	16 (14.0)	0 (0)	
Female gender [n (%)]	76 (68.0)	20 (61.0)	0.439
Epilepsy etiology [n (%)]			
Unknown	50 (45.0)	14 (42.0)	0.005
Infectious	3 (2.7)	0 (0)	
Genetic	18 (16.0)	15 (45.0)	
Immune	2 (1.8)	0 (0)	
Metabolic	16 (14.0)	0 (0)	
Structural	23 (21.0)	4 (12.0)	
Atopic diseases [n (%)]	14 (12.0)	19 (58.0)	< 0.001
Family history of drug allergy [n (%)]	9 (8.0)	23 (70.0)	< 0.001
Days after drug initiation/dose increase [n (%)]	2 (1.4)	3 (2.3)	0.100
Dose increase [n (%)]	27 (24.0)	4 (12.0)	0.140
Multiple ASMs [n (%)]	10 (8.9)	23 (69.7)	< 0.001
The route of administration [n (%)]			0.068
Intravenous	12 (11.0)	0 (0)	
Per oral	100 (89.0)	33 (100)	
Biochemical characteristics of the first CAR-related ASMs [n (%)]			< 0.001
Aromatic	58 (52.0)	31 (93.9)	
Nonaromatic	54 (48.0)	2 (6.1)	
Immediate (< 1 hour after administration) reaction	7 (6.2)	1 (3.0)	0.700
Rash severity [n (%)]			
Mild	101 (90.0)	27 (82.0)	0.200
Severe CAR	11 (9.8)	6 (18.0)	
SJS	8 (7.1)	4 (12.0)	0.300
DRESS	3 (2.7)	2 (6.1)	
Biochemical characteristics of new ASMs [n (%)]			< 0.001
Aromatic	19 (17.0)	23 (70.0)	
Nonaromatic	93 (83.0)	10 (30.0)	
Biochemical characteristics of the first CAR-related ASMs and new ASMs [n (%)]			< 0.001
Aromatic + nonaromatic	73 (65.0)	12 (36.0)	
Both aromatic	2 (1.8)	21 (64.0)	
Both nonaromatic	37 (33.0)	0 (0)	

*Mann-Whitney U test, Fisher's exact test, Pearson's chi-squared test; **Group 1 includes the patients with only one history of rash, while group 2 includes the patients with ASM-related CAR recurrence.
ASM: Anti-seizure medication; CAR: Cutaneous adverse reaction; SJS: Stevens-Johnson syndrome; DRESS: Drug reaction with eosinophilia and systemic symptoms; IQR: Interquartile range

The most common CAR-related ASMs in group 1 were valproate (n = 33, 29.5%), carbamazepine (n = 22, 19.6%), and oxcarbazepine (n = 14, 12.5%), while the first CARs were mostly caused by carbamazepine (n = 23, 69.7%) and lamotrigine (n = 4, 12.1%) in group 2 (Figure 1). Patients whose initial rash was due to an ASM with an aromatic ring had a statistically higher rate of rash recurrence (94% vs. 52%, P < 0.001, OR: 14.4, 95% CI: 3.2-63.2). The aromatic nature of the newly started ASM was found to be another risk factor for rash recurrence (P < 0.001, OR: 11.3, 95% CI: 4.6-27.5) (Figure 2).

Discussion

CARs are a substantial reason of apprehension when ASMs are initiated, titrated, modified, and combined to achieve better seizure control. In fact, these reactions have been reported in approximately 3% to 16% of patients using ASM.[8]

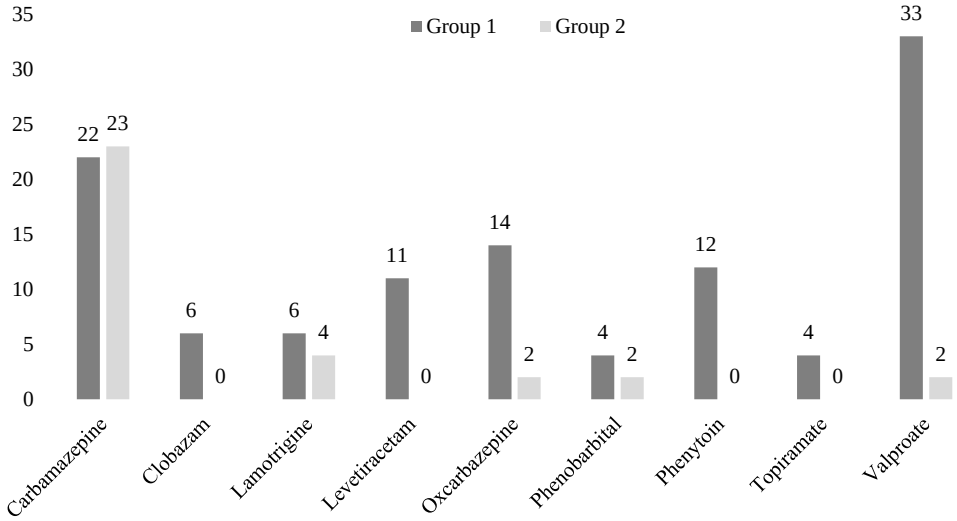

Figure 1. Anti-seizure medications (ASMs) in the patients with a single rash (group 1) and a rash recurrence (group 2)

Immediate withdrawal of drug is the most fundamental step in the management of CAR; however, the need for ASM is often longer-lasting in the pediatric population than in adults, and such complete discontinuations greatly reduce medication options in the pediatric age group for whom currently approved drugs are scarce. Previous studies evaluating risk and predisposing factors of ASM-related CAR usually composed of adult cohorts, and very little was known in the literature on the behalf of pediatric patients.[8,9] This study set out with the aim of assessing the demographic and clinical risk factors associated with CAR in a pediatric cohort, especially in patients with cross-reactivity (a second CAR with a second ASM).

History of a previous CAR related to ASM is the most important indicator of a future rash with up to 25.0% increased risk.[3,10] In accordance with the previous results, the present study demonstrated 22.8% rash recurrence. ASM-related CAR has been found to be particularly associated with advanced age due to mainly decreasing liver volume, blood flow, and metabolism.[10] A multivariate logistic regression analysis of ASM in pediatric patients found that one of the greatest risk factors for the development of rash was being younger than 12 years of age.[11] Consistent with the literature, the median age of our patients with a single rash was 60 (IQR: 27-100) months; however, no significant difference was found between the control group.

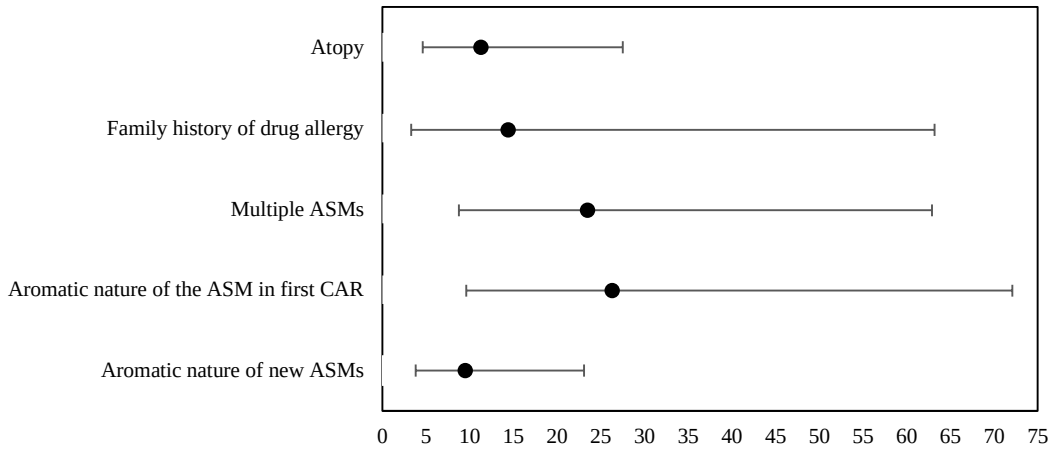

Figure 2. Risk factors for a second cutaneous adverse reaction (CAR) due to anti-seizure medications (ASMs) [the intervals on the horizontal axis represent the confidence interval (CI). The values in each node show odds ratio (OR).]
ASM: Anti-seizure medication, CAR: Cutaneous adverse reaction

In a study conducted in China, four of 18 patients with ASM cross-reactivity were pediatric patients, with a median age of 11.5 years. In our study, the median age of patients with cross-reactivity was slightly lower, being 84 (IQR: 13-96) months. However, due to the small number of patients in both studies, larger cohort studies are needed to determine whether age is a risk factor for ASM-related CAR recurrence. Patients with ASM-related CAR have a female gender predominance, with more than twice the frequency of males.[10] In the study of Guvenir et al.,[11] although the male gender was more common in pediatric patients with ASM-related CAR, no significant difference was found between the sexes in the regression analysis. In a study evaluating patients with ASM cross-reactivity, female gender was again more common with a rate of 61.11%.[3] Indeed, the gender data of our study corroborate the findings of a great deal of these previous studies, with 68% of the patients with a single rash and 61% of patients with rash recurrence being female. Although female gender was significantly higher in patients with a single rash compared to the control group, gender was not a risk factor for rash recurrence. Very little is currently known about allergic conditions in patients with epilepsy, particularly in children. Two large Canadian health surveys evaluating somatic comorbidities in epilepsy revealed that allergies were the most common comorbidity in patients with epilepsy with a rate of 32.8%, which was slightly higher than in the general population.[12]

In another study, the rate of allergic diseases was found to be similar with 30.5% in patients with ASM-related hypersensitivity reactions.[13] In a health survey in the United States of America (USA), lifetime asthma prevalence and one-year prevalence of asthma, atopic dermatitis, allergic rhinitis, and food allergies were all associated with increased odds of ever being diagnosed with epilepsy.[14] In contrast to earlier findings, however, no evidence of significant relationship between ASM-related hypersensitivity reactions and other allergic reactions including allergic rhinitis (7.3%), allergy to specific food (5.4%), allergic asthma (1.8%), and atopic dermatitis (0%) was detected in a more recent report.[13] In a pediatric cohort, personal or family history of atopic diseases was reported to have no significant correlation with ASM-related CARs.[15] As far as we know, there is no study evaluating the relationship between ASM cross-reactivity in pediatric patients and other allergic diseases or a family history of drug allergy. In our study, neither atopic diseases nor familial drug allergy was statistically and significantly associated with a single rash; however, both were significant risk factors for rash recurrence.

Monotherapy is sufficient for seizure-freedom in 70% of patients with epilepsy; however, the remaining 30% develop a drug-resistant epilepsy, leading the need for polytherapy.[16] Polytherapy has been reported as a risk factor for ASM-related hypersensitivity reactions in children, posing an even greater challenge to the physician in the management of epilepsy.[17] Another prospective multivariate logistic regression analysis of ASM use in 570 children demonstrated that one of the greatest risk factors for developing rash was polytherapy. In fact, the polytherapy was reported in 9.9% of ASM-related hypersensitivity reactions.[11] In our study, polytherapy was at a similar rate with 8.9% in patients with a single rash. However, to the best of our knowledge, there is no study examining the association of polytherapy with ASM-related rash recurrence in children. We found a 23.5-fold increased risk of rash recurrence in the use of polytherapy.

Numerous sources point at aromatic ASMs which contribute to a large extent to eliciting CARs, ranging from 61.3% to 74.2%.[5,9,11,18] In our study, although the rate of aromatic ASMs was higher in patients with a single rash, there was no significant difference compared to the control group. In our study, the rate of aromatic ASMs was higher in patients with a single rash compared to the control group, but no significant difference was obtained. On the other hand, aromatic ASMs were detected in the first reaction in 93.9% of patients with rash recurrence, which increased the risk of cross-reactivity 14.4 times. Moreover, the aromatic nature of the newly started ASM after the first rash also increased the rash recurrence 11.3 times. Cross-sensitivity between aromatic ASMs is estimated to occur clinically in 40%-58% of patients, while in vitro tests demonstrate rates of up to 80%.[10] Accordingly, we demonstrated that rash recurrence was significantly higher when the first CAR-related ASMs and new ASMs were both aromatic.

Although aromatic ASMs are more common in the etiology of CAR, non-aromatic ASMs may rarely cause rash. The rash incidence in patients using valproate is 1%-5%.[10] Rather than an aromatic ASM, valproate was the most common CAR-related ASM (29.5%) in patients with a single rash in this study probably due to higher

rank in drug choice compared to others. Although valproate is considered to be a low-risk drug for ASM-related CAR, when used in combination therapy, rash rate significantly increases due to its metabolic properties as an inhibitor of cytochrome P450 (CYP) isoenzymes leading to increased plasma concentration of aromatic ASMs and their metabolites.[11] Accordingly, valproate was lower among the ASMs causing rash recurrence, while aromatic drugs were significantly higher whether they were used as monotherapy or polytherapy.

When several ASMs including carbamazepine, phenytoin, and lamotrigine are started at a low dose and increased gradually, the risk of allergic reactions including CAR is reduced, possibly because slow titration allows for desensitization.[8,10] As far as we know, there is no study examining the difference between initiation of ASM or increasing the dose and recurrence of rash in the pediatric age group. In the present study, dose increase or new initiation of ASM was not associated with a significant difference in rash recurrence.

Conclusion

Atopic diseases, family history of drug allergy, polytherapy, the aromatic nature of the ASMs associated with the first rash, and the aromatic nature of newly added ASMs after a CAR were risk factors for a rash recurrence. A detailed history of allergic entities and careful approach to aromatic drugs can prevent recurrence of CARs. Further studies with larger drug-specific cohorts would be worthwhile to establish the risk factors of rash recurrence due to certain ASMs.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

None.

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