

# The Frequency and Clinical Features of Hypersensitivity Reactions to Antiepileptic Drugs in Children: A Prospective Study



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**What is already known about this topic?** Although hypersensitivity reactions to antiepileptic drugs (AEDs) are less frequent than antibiotics and nonsteroidal anti-inflammatory drug hypersensitivity, AEDs are important because they are a major cause of severe cutaneous adverse reactions.

**What does this article add to our knowledge?** There is very little information on AED hypersensitivity in children. In our study, hypersensitivity reactions to AEDs developed in 5.4% of the patients.

**How does this study impact current management guidelines?** According to our results, children who are younger than 12 years, who use multiple AEDs, and who use aromatic AEDs more frequently experience AED hypersensitivity. Therefore, these patients should be monitored more carefully for drug reactions including severe cutaneous adverse reactions.

**BACKGROUND:** Antiepileptic drugs (AEDs) can cause hypersensitivity reactions during childhood. Studies report a wide clinical spectrum of reactions with AED use, ranging from a mild rash to severe cutaneous reactions.

**OBJECTIVE:** To determine the prevalence and clinical features of AED hypersensitivity reactions during childhood.

**METHODS:** Patients in our pediatric neurology clinic who were prescribed an AED for the first time between November 2015 and November 2016 were monitored and those who developed skin rash during this period were evaluated.

**RESULTS:** A total of 570 patients were evaluated. The median age of the patients was 8.86 (interquartile range, 4.2-13.7) years, and 55.8% (318) of patients were male. The most frequently

used AEDs were valproic acid (42%,  $n = 285$ ) and carbamazepine (20.4%,  $n = 116$ ). Hypersensitivity reactions to AEDs developed in 5.4% of patients. Of these patients, 71% (29) had cutaneous drug reactions and 29% (9) had severe cutaneous drug reactions; 61.3% (19) were using aromatic AEDs, and the leading suspected AED was carbamazepine (45.2%).

Comparison of patients who did and did not develop AED hypersensitivity showed that hypersensitivity was more frequent among patients who were younger than 12 years, who used aromatic AEDs, or who used multiple AEDs. In addition, according to regression analysis results, aromatic AED use significantly increased the risk of AED hypersensitivity ( $P < .001$ ).

**CONCLUSIONS:** Although allergic reactions to AEDs are rare, they are of significance because they can cause life-threatening severe cutaneous drug reactions. Therefore, patients receiving AEDs, especially aromatic AEDs, must be monitored closely. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:2043-50)

**Key words:** Antiepileptic drugs; Child; DRESS; Epilepsy; Hypersensitivity; SJS; Patch test

## INTRODUCTION

Drug hypersensitivity reactions in children were demonstrated to be most frequently associated with antibiotics (especially the beta-lactam group) and nonsteroidal anti-inflammatory drugs (NSAIDs).<sup>1</sup> Antiepileptic drugs (AEDs) were also found to cause hypersensitivity reactions during childhood. Although hypersensitivity reactions to AEDs are less frequent than antibiotics and nonsteroidal anti-inflammatory drug hypersensitivity, AEDs are important because they are a major cause of severe cutaneous

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*Abbreviations used*

|               |                                                          |
|---------------|----------------------------------------------------------|
| <i>AED-</i>   | <i>Antiepileptic drug</i>                                |
| <i>AED-H-</i> | <i>AED hypersensitivity</i>                              |
| <i>DRESS-</i> | <i>Drug rash with eosinophilia and systemic symptoms</i> |
| <i>IQR-</i>   | <i>Interquartile range</i>                               |
| <i>NSAID-</i> | <i>Nonsteroidal anti-inflammatory drug</i>               |
| <i>SCAR-</i>  | <i>Severe cutaneous adverse reaction</i>                 |
| <i>SJS-</i>   | <i>Stevens-Johnson syndrome</i>                          |
| <i>TEN-</i>   | <i>Toxic epidermal necrolysis</i>                        |

adverse reactions.<sup>2</sup> Furthermore, epileptic patients are in need of these drugs and alternatives may not always be as effective. Thus, it is important to determine whether the reaction is a true hypersensitivity, and if it is, we have to understand the reactions better for better management.<sup>2</sup>

The incidence of rash associated with AEDs is reported to be 5% to 17%, and the incidence of AED-associated SCARs is between 1 per 1,000 to 1 per 10,000.<sup>3</sup> AEDs that most commonly cause a rash are of aromatic type such as carbamazepine, phenytoin, and lamotrigine.<sup>4</sup> Advanced age and the female sex were also indicated to pose a risk for AED-H in adult studies.<sup>5</sup> However, there are very few studies on AED-H in children.

The mechanism by which AEDs induce hypersensitivity is unknown. AEDs are considered to be of low immunogenicity according to the hapten hypothesis because their molecular weight is less than 1 kDa, but AEDs containing an aromatic ring in their chemical structure are considered to form an arene oxide intermediate that may become immunogenic through interactions with proteins or cellular macromolecules. Noncovalent binding of the drug to the T-cell receptor of specific T-cell clones is the other mechanism of drug hypersensitivity. Drug-specific T cells have been identified for lamotrigine and carbamazepine.<sup>6</sup>

This study aimed to determine the frequency and clinical features of AED-H in children who were using AEDs for the first time.

## METHODS

### Patients

The study was conducted between November 1, 2015, and October 30, 2016, in the Pediatric Allergy and Neurology Clinics of Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital, University of Health Sciences, Ankara, Turkey. It was approved by the hospital's clinical research ethics committee. During the study period, patients aged 18 years or younger in whom an AED was initiated for the first time in our pediatric neurology clinic were enrolled. Those patients who had skin rash during AED use were evaluated for AED-H.

### Study procedures

The age, sex, diagnosis of the patient, the AED used, whether another drug was used concurrently, history of allergic disease, drug allergy history of the family, accompanying symptoms, and the time interval between the initiation of suspected AED and the emergence of hypersensitivity symptoms due to the suspected AED were recorded. If a single AED was being used, this AED was considered the suspected drug and patients were questioned about whether there was a dose increase in the last 8 weeks. If multiple AEDs were

used, the newly added AED or the AED whose dose was increased in the last 8 weeks was considered as the suspected drug. Reactions occurring within the first hour were labeled as "immediate reactions"; the ones occurring later were labeled as "nonimmediate reactions." In addition, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, and lamotrigine were recorded as "aromatic," whereas other AEDs were recorded as "nonaromatic."

A detailed physical examination of the patients was also performed. The skin findings were recorded according to their localizations and characteristics. In the patients with mucosal involvement, the involved mucosa was recorded. In the patients with lymphadenopathy, the localization and size of the lymph nodes, possible organomegaly (hepatomegaly and/or splenomegaly), and vital signs (body temperature, pulse, and blood pressure) were recorded.

Complete blood cell count, peripheral blood smear, acute-phase reactants (sedimentation and C-reactive protein), liver and kidney function tests, urinalysis, cultures (throat, blood, and urine), viral serologic tests (Epstein-Barr virus viral capsid antigen IgM, cytomegalovirus IgM, herpes simplex virus type I IgM, toxoplasma IgM, rubella IgM, hepatitis B surface antigen, anti-hepatitis B surface antibody, and anti-hepatitis B core antibody), and bacterial serologic tests (Mycoplasma IgM and Chlamydia IgM) were performed for differential diagnosis.

When AED-H was not considered, the AEDs were not discontinued, but when AED-H was considered, the AEDs of the patients were discontinued. These patients were first evaluated for compliance with the SCAR criteria. The possibility of drug rash with eosinophilia and systemic symptoms (DRESS) syndrome was evaluated using the Registry of Severe Cutaneous Adverse Reactions scoring system on the basis of the presence of mucocutaneous rash, fever, lymphadenopathy, and hematological anomalies such as eosinophilia, atypical lymphocytes, and internal organ involvement.<sup>7</sup> Acute onset of mucous membrane involvement (at least 2 mucosal surfaces) and skin symptoms (maculae, target-like, bullae or erosion, and positive Nikolsky sign) together with epidermal detachment of less than 10% of the total body surface area are regarded as Stevens-Johnson syndrome (SJS).<sup>8</sup> Epidermal detachment of more than 30% of the total body surface area together with similar clinical signs is classified as toxic epidermal necrolysis (TEN) and that of 10% to 30% as SJS/TEN overlap.<sup>8</sup>

All patients who were considered to have SCARs were hospitalized. Systemic steroids and/or intravenous immunoglobulin were administered. However, in patients who were considered to have a mild cutaneous drug reaction, the suspected AEDs were discontinued and antihistamine drugs were prescribed. These patients came to the outpatient allergy clinic daily to evaluate the progress of the reaction.

### Allergy workup

**Patch test.** In the patients who were considered to have AED-H and who had delayed reaction, patch test was carried out with the suspected AED at least 6 weeks after the reaction. Informed consent was obtained from the families. Patch testing was performed with all the AEDs the patient was using at the time of the reaction. In the patch test, the drug was put in an aluminum chamber (Finn chamber) by preparing a homogeneous mixture with petrolatum so that it would contain the active drug at a certain concentration (1% and 10% concentrations were used for each AED) and was then adhered to the patient's back.<sup>2</sup> Petrolatum was used as a negative control. After 48 hours, the patch was opened and evaluated. If there

was no reaction, it was re-evaluated after 72 hours. Parents were instructed to check their children's back for reactions that could occur within 1 week and to contact the clinic if there was any reaction. If there was no reaction, the result was considered as negative, but if there was a reaction, the result was considered as positive.<sup>9</sup>

**Drug provocation test.** Drug provocation test was planned for patients with a mild cutaneous drug reaction and immediate reaction. A provocation test involved administering the suspected drug at divided doses every 30 minutes, until a cumulative dose close to the age-/weight-adjusted daily dose of the drug was achieved. The drug was given maximally in 5 doses to prevent the possibility of patient desensitization. The test was discontinued in the event of any reaction. Administration was open and performed by a physician with full resuscitation backup.<sup>10</sup>

### Statistical analysis

Statistical analyses were performed using SPSS 22.0 (IBM SPSS Statistics, Chicago, Ill). Descriptive statistics were expressed as mean  $\pm$  SD or median (minimum-maximum) for continuous variables and as case numbers and percentage for nominal variables. The Shapiro-Wilk test was used to investigate whether the distribution of continuously measured variables was close to normal. Whether there was a difference between the parameters of patients with AED-H and those with no AED-H or between the parameters of patients with mild cutaneous drug reactions and those with severe cutaneous drug reactions due to epileptic drugs was assessed by chi-square test and the Fisher exact test. Multivariate logistic regression was used to determine which variables related to the occurrence of AED-H were independent risk factors. The results were considered statistically significant when  $P$  was less than .05.

## RESULTS

The study evaluated 570 patients who used AEDs. The median (interquartile range [IQR]) age of the patients was 8.86 (4.21-13.76) years and 55.8% (318) were male. Of the patients, 84% (479) used a single AED and 16% (91) used multiple AEDs. Of the patients, 35.5% (202) used aromatic, 54% (308) used nonaromatic, and 10.5% (60) used aromatic and nonaromatic AEDs. The number of AEDs received by the 570 patients was 679, with valproic acid (42%, 285 of 679) being the most common and carbamazepine in second place (17%, 116 of 679).

Skin rash was found to develop in 6.8% (39) of the patients. Only 1 of these patients described an immediate reaction: a maculopapular rash that occurred on the face on the second day of clobazam therapy. It started 5 minutes after the drug ingestion and spontaneously resolved within 30 minutes. Oral provocation test result was negative. The patient still continues to use this drug without any problem.

The skin rash was found to be associated with infection in 6 patients (scarlet fever in 3 patients, hand-foot-mouth disease in 2 patients, and infectious mononucleosis in 1 patient) and with bug bite in 1 patient. The AEDs used by these patients were not discontinued. These patients who were treated properly for infections still continue to use their AEDs without any problem.

### Characteristics of the patients in whom AED-H was considered

AED-H was considered in the remaining 31 (5.4%) patients. The median (IQR) age was 7.3 (2.8-11.0) years and 61.3% (19) were male. None of these patients used another

drug concurrently with the AED. Of these patients, 71% (22) used a single AED and 61.3% (19) used aromatic AEDs (Table I). The time between the initiation of suspected AED and the emergence of clinical findings was  $28.55 \pm 32.62$  (minimum-maximum: 7-180; median [IQR], 20 [12-30]) days. All the patients had maculopapular rash as the skin lesion. In 64.5% (20) of the patients, the rash was generalized. There were also target-like lesions in 5 (16.1%) patients and mucosal involvement in 5 (16.1%) patients. Of the patients, 45.2% (14) had eosinophilia, 48.4% (15) had elevation in acute-phase reactants, and 25.8% (8) had impaired liver function test results. Of 31 patients, 71% (22) were treated for mild cutaneous drug reaction and 29% (9) were treated for SCARs. Of these patients, 5 were diagnosed with SJS and 4 were diagnosed with DRESS syndrome (Table I).

Of the patients who were using a single AED, 3.8% (18 of 479) had a mild cutaneous reaction, whereas 0.8% (4 of 479) had SCARs (0.4% had SJS and 0.4% had DRESS syndrome). When patients who were using multiple AEDs were evaluated, 4.4% (4 of 91) had mild cutaneous reactions and 5.5% (5 of 91) developed SCARs (3.3% had SJS and 2.2% had DRESS syndrome) (Table I). The demographic characteristic of the patients who used multiple AEDs and developed AED-H are presented in Table II.

At the time of the reaction development, the serum AED levels (with phenytoin, phenobarbital, carbamazepine, and valproic acid) were in the recommended therapeutic range. However, the serum levels of all the AEDs could not be measured.

No deaths occurred in this series.

### Comparison of patients with and without AED-H

There was no difference in terms of age and sex between patients with and without AED-H. The incidence of drug hypersensitivity was found to be higher in patients who used multiple AEDs and aromatic AEDs (Table III). Of the patients, 6.9% (26) who were younger than 12 years and 2.6% (5) of patients who were 12 years or older developed AED-H ( $P = .03$ ). As a result, those who were younger than 12 years, those who used aromatic AEDs, and those who used multiple AEDs were found to have a higher rate of AED-H. When the regression analysis was performed, it was observed that the main risk factor for AED hypersensitivity was the use of aromatic AEDs ( $P < .001$ ) (Table IV).

### Comparison of patients with mild cutaneous and severe cutaneous drug reactions

There was no statistically significant difference between the 2 groups in terms of age, sex, and duration of drug use. It was observed that the patients who used multiple AEDs had higher rates of SCARs ( $P = .037$ ) (Table V).

### Assessment of the test results of the patients in whom the diagnostic test was performed

Patch test was performed for a total of 39 drugs in 29 of 31 patients, from whom informed consent was obtained. Of the 29 patients who were tested, 17 (58.6%) had a positive patch test result. Of the 39 patch tests, results for 17 (43.6%) were positive. Of the 25 patch tests performed on 21 patients with mild cutaneous drug reactions, results for 11 (44%) were positive. Of the 14 patch tests performed on 8 patients with SCARs, results for 6 (42.9%) were positive. Results for 11 of 15 (73.3%) patch

TABLE I. Characteristics of patients with AED-H

| Etiology                                 | Total exposure, n | AED-H, n (%) | Mild cutaneous reaction, n (%) | Severe cutaneous reaction, n (%) |                |
|------------------------------------------|-------------------|--------------|--------------------------------|----------------------------------|----------------|
|                                          |                   |              |                                | SJS                              | DRESS syndrome |
| AEDs based on their combination          |                   |              |                                |                                  |                |
| Single AED                               | 479               | 22 (4.6)     | 18 (3.8)                       | 2 (0.4)                          | 2 (0.4)        |
| Valproic acid                            | 237               | 4 (1.7)      | 4                              | —                                | —              |
| Carbamazepine                            | 102               | 10 (9.8)     | 7                              | 2                                | 1              |
| Phenobarbital                            | 65                | 7 (10.7)     | 6                              | —                                | 1              |
| Phenytoin                                | 4                 | 1 (25)       | 1                              | —                                | —              |
| Multiple AEDs                            | 91                | 9 (9.9)      | 4 (0.8)                        | 3 (3.3)                          | 2 (2.2)        |
| Phenobarbital + levetiracetam            | 8                 | 1 (12.5)     | 1                              | —                                | —              |
| Valproic acid + carbamazepine            | 8                 | 4 (50)       | 1                              | 1                                | 2              |
| Valproic acid + oxcarbazepine            | 6                 | 1 (16.7)     | 1                              | —                                | —              |
| Valproic acid + clobazam                 | 3                 | 1 (33.3)     | —                              | 1                                | —              |
| Phenobarbital + carbamazepine            | 1                 | 1 (100)      | 1                              | —                                | —              |
| Valproic acid + topiramate + lamotrigine | 1                 | 1 (100)      | —                              | 1                                | —              |
| AEDs based on their chemical structure   |                   |              |                                |                                  |                |
| Aromatic                                 | 202               | 19 (9.4)     | 15 (7.4)                       | 2 (1)                            | 2 (1)          |
| Carbamazepine                            | 102               | 10 (9.8)     | 7                              | 2                                | 1              |
| Phenobarbital                            | 65                | 7 (10.8)     | 6                              | —                                | 1              |
| Phenytoin                                | 4                 | 1 (25)       | 1                              | —                                | —              |
| Phenobarbital + carbamazepine            | 1                 | 1 (100)      | 1                              | —                                | —              |
| Nonaromatic                              | 308               | 5 (1.6)      | 4 (1.3)                        | 1 (0.3)                          | —              |
| Valproic acid                            | 237               | 4 (1.7)      | 4                              | —                                | —              |
| Valproic acid + clobazam                 | 3                 | 1 (33.3)     | —                              | 1                                | —              |
| Aromatic + nonaromatic                   | 60                | 7 (11.7)     | 3 (5)                          | 2 (3.3)                          | 2 (3.3)        |
| Phenobarbital + levetiracetam            | 8                 | 1 (12.5)     | 1                              | —                                | —              |
| Valproic acid + carbamazepine            | 8                 | 4 (50)       | 1                              | 1                                | 2              |
| Valproic acid + oxcarbazepine            | 6                 | 1 (16.7)     | 1                              | —                                | —              |
| Valproic acid + topiramate + lamotrigine | 1                 | 1 (100)      | —                              | 1                                | —              |

tests with carbamazepine, 3 of 11 (27.3%) patch tests with valproic acid, 2 of 7 (28.6%) patch tests with phenobarbital, and 1 (100%) patch test with lamotrigine were positive (Table VI). Positivity in the patch test was seen at only 10% concentration for all drugs and not 1%.

## DISCUSSION

To our knowledge, this is the first prospective study that investigates hypersensitivity reactions to AEDs in children. The frequency of hypersensitivity reactions in patients in whom an AED was initiated for the first time was found to be 5.4% (31 of 570). Of these reactions, 19% were SCARs and 71% were mild cutaneous drug reactions. The most common suspected AEDs were carbamazepine and phenobarbital. None of our patients having confirmed AED-H had immediate reactions. The patch test results were positive in 58.6% of the patients who could be tested.

AEDs have been reported to cause hypersensitivity reactions within a broad clinical spectrum from mild skin rash to SCARs, which are associated with severe mortality and morbidity.<sup>2</sup> The incidence of rash and severe cutaneous reactions with AEDs is about 5% to 17% and between 1 per 1,000 to 1 per 10,000, respectively.<sup>3</sup> However, there are no clear data on the incidence of AED-H in children. Frequency of rash was 3.8% in our study, which is in accordance with that reported in the literature.<sup>4</sup> However, the frequency of SCARs was considerably higher

(1.5%) in our study. Therefore, children must be monitored carefully for severe reactions while using AEDs.

All available data come from studies evaluating adverse reactions due to AEDs, and to our knowledge there are no reports dealing specifically with hypersensitivity reactions to AEDs in children. In the literature, there are 2 studies (from the United Kingdom and Turkey) in which the pediatric patients who used AEDs were evaluated in terms of adverse reactions.<sup>11,12</sup> Anderson et al<sup>11</sup> evaluated 180 children for adverse drug reactions to AEDs and reported that 9 patients had a skin rash and 2 patients had SJS. The rate of AED-H was 6.1% (11 of 180). The characteristics of the rash were not defined. Patients did not undergo further examination for drug hypersensitivity. The most common AED resulting in a rash was carbamazepine, and drugs causing SJS were phenytoin and phenobarbital—all aromatic AEDs.<sup>11</sup>

In another study from our country, Yilmaz et al<sup>12</sup> evaluated AED adverse reactions in 289 children who were newly diagnosed with epilepsy and received AED monotherapy for at least 12 months. The most commonly used AEDs in this study were valproic acid (49.1%) and carbamazepine (14.5%). They have reported that 3 (1%) patients using carbamazepine had maculopapular skin rash. Two of them needed cessation of the drug and in 1 patient the drug was continued with dose reduction. Patients were not evaluated with allergy workup.

**TABLE II.** Demographic characteristics of patients who use multiple AEDs and develop AED-H

| Patient no. | Age (y) | Sex    | Diagnosis                    | AEDs used                                |
|-------------|---------|--------|------------------------------|------------------------------------------|
| 1           | 3.60    | Female | SJS                          | Valproic acid + topiramate + lamotrigine |
| 2           | 6.10    | Female | SJS                          | Valproic acid + clobazam                 |
| 3           | 10.9    | Female | SJS                          | Valproic acid + carbamazepine            |
| 4           | 13.70   | Male   | DRESS syndrome               | Valproic acid + carbamazepine            |
| 5           | 11.90   | Male   | DRESS syndrome               | Valproic acid + carbamazepine            |
| 6           | 13.5    | Male   | Mild cutaneous drug reaction | Valproic acid + carbamazepine            |
| 7           | 13.8    | Male   | Mild cutaneous drug reaction | Valproic acid + oxcarbazepine            |
| 8           | 3.1     | Female | Mild cutaneous drug reaction | Phenobarbital + carbamazepine            |
| 9           | 2       | Female | Mild cutaneous drug reaction | Phenobarbital + levetiracetam            |

**TABLE III.** Comparison of patients with and without AED-H

| Characteristic                                | Patient with AED-H | Patient without AED-H | P value |
|-----------------------------------------------|--------------------|-----------------------|---------|
| Age (y), median (IQR)                         | 7.30 (2.8-11.0)    | 8.95 (4.29-13.93)     | .07     |
| Sex, male, n (%)                              | 19 (61.3)          | 299 (55.5)            | .52     |
| AED therapy, n (%)                            |                    |                       |         |
| Single (n = 479)                              | 22 (4.6)           | 457 (95.4)            | .04     |
| Multiple (n = 91)                             | 9 (9.9)            | 82 (90.1)             |         |
| AEDs based on their chemical structure, n (%) |                    |                       |         |
| Aromatic (n = 202)                            | 19 (9.4)           | 183 (90.6)            | <.001   |
| Nonaromatic (n = 308)                         | 5 (1.6)            | 303 (98.4)            |         |
| Aromatic + nonaromatic (n = 60)               | 7 (11.7)           | 53 (88.3)             |         |

**TABLE IV.** Results of logistic regression analyses for independent predictors of AED-H

| Predictor            | P value | Odds ratio | 95% CI |        |
|----------------------|---------|------------|--------|--------|
|                      |         |            | Lower  | Upper  |
| Younger than 12 y    | .103    | 2.278      | 0.848  | 6.123  |
| Sex                  | .390    | 1.396      | 0.652  | 2.989  |
| Use of multiple AEDs | .312    | 1.540      | 0.667  | 3.552  |
| Use of aromatic AEDs | <.001   | 5.900      | 2.198  | 15.839 |
| Constant             | <.001   | 0.003      |        |        |

In our study, 84% of the patients used a single AED, and the most commonly used AEDs were valproic acid (50%) and carbamazepine (20.4%) in accordance with the aforementioned 2 studies. The results of our study are similar to those of the study by Anderson et al.<sup>11</sup> However, when compared with the results of the study by Yilmaz et al,<sup>12</sup> a noteworthy finding was that the rate of AED-H reactions in our study was higher. This may have resulted from the fact that the patients in the study of Anderson et al were all using monotherapy, but 29% (9 of 31) of our patients were using multiple drug therapy during the reaction. In the present study, we have demonstrated that patients who used more than 1 drug had reactions more frequently.

In our study, 9.9% (9 of 91) of patients who used multiple AEDs and 4.6% (22 of 479) of patients who used a single AED developed mild cutaneous reactions. Also, 5.5% (5 of 91) of patients who used multiple AEDs and 0.8% (n = 4) of patients who used a single AED developed SCARs. Therefore, both mild cutaneous reaction and SCAR development rates were higher in

the patients who used multiple AEDs. Drugs used together may affect each other's metabolism and this may increase the risk of AED-H.<sup>2,3,6</sup>

Advanced age has been reported as a risk factor for AED-H in adult studies.<sup>5</sup> However, there have been no clear data in the pediatric age group. Contrary to adult studies, we observed that AED-H occurred more commonly in patients who were younger than 12 years, and use of aromatic drugs was also more common in this age group. When we put the data into regression analysis, age was not found to be a risk factor. We have also found a higher frequency of AED-related SCARs in children than in previous adult studies. A previous study by Chan et al<sup>5</sup> has also reported that AED-related SCARs were more frequent in children younger than 12 years. As is known, the risk of many drug reactions is age-related, and there are age-related differences in drug metabolism. In particular, the reduction in glucuronide conjugation in young infants and the faster rates of cytochrome P450 (CYP)-mediated reactions in infants and children compared with adults may result in increased production of reactive metabolites and increased susceptibility of hypersensitivity reactions in children.<sup>6,13,14</sup>

In previous studies it was indicated that aromatic AEDs were the most common cause of AED-H and that SCARs developed most commonly with aromatic AEDs.<sup>4,14,15</sup> Aromatic AEDs were responsible in 64.4% of patients with cutaneous reactions due to AEDs in the study by Handoko et al.<sup>16</sup> Similarly, in our study, the suspected AED was of an aromatic type in 74.2% (23 of 31) of patients.

In our study, the most common AED causing hypersensitivity reaction was carbamazepine. Drug hypersensitivity developed in 12.9% (15) of patients who used carbamazepine; of those, 7.8%

**TABLE V.** Comparison of the patients with mild cutaneous and severe cutaneous drug reactions

| Characteristic                                | Mild cutaneous reactions | Severe cutaneous reactions | P value |
|-----------------------------------------------|--------------------------|----------------------------|---------|
| Age (y), median (IQR)                         | 7.25 (2.60-10.65)        | 9.80 (4.85-11.45)          | .51     |
| Sex: male, n (%)                              | 14 (63.6)                | 5 (55.6)                   | .675    |
| AED therapy, n (%)                            |                          |                            |         |
| Single                                        | 18 (81.8)                | 4 (44.4)                   | .037    |
| Multiple                                      | 4 (18.2)                 | 5 (55.6)                   |         |
| AEDs based on their chemical structure, n (%) |                          |                            |         |
| Aromatic                                      | 15 (68.2)                | 4 (44.4)                   | .57     |
| Nonaromatic                                   | 4 (18.2)                 | 1 (11.2)                   |         |
| Aromatic + nonaromatic                        | 3 (13.6)                 | 4 (44.4)                   |         |

**TABLE VI.** Patch test results of patients

| AED           | AEDs used in patch testing, n | Positivity rate in patch test, n (%) | Positivity rate in patch test by reaction type |                                     |                        |
|---------------|-------------------------------|--------------------------------------|------------------------------------------------|-------------------------------------|------------------------|
|               |                               |                                      | Mild cutaneous reactions (n = 25)              | Severe cutaneous reactions (n = 14) |                        |
|               |                               |                                      |                                                | SJS                                 | DRESS syndrome         |
|               |                               |                                      |                                                |                                     |                        |
|               |                               |                                      | Positive patch test, n                         | Positive patch test, n              | Positive patch test, n |
| Valproic acid | 11                            | 3 (27.3)                             | 2                                              | 1                                   | —                      |
| Carbamazepine | 15                            | 11 (73.3)                            | 7                                              | 1                                   | 3                      |
| Phenobarbital | 7                             | 2 (28.6)                             | 2                                              | —                                   | —                      |
| Levetiracetam | 1                             | —                                    | —                                              | —                                   | —                      |
| Oxcarbazepine | 1                             | —                                    | —                                              | —                                   | —                      |
| Topiramate    | 1                             | —                                    | —                                              | —                                   | —                      |
| Phenytoin     | 1                             | —                                    | —                                              | —                                   | —                      |
| Lamotrigine   | 1                             | 1 (100)                              | —                                              | 1                                   | —                      |
| Clobazam      | 1                             | —                                    | —                                              | —                                   | —                      |
| Total, n (%)  | 39                            | 17 (43.5)                            | 11 (44)                                        | 3 (21.4)                            | 3 (21.4)               |

(9) had mild cutaneous drug reactions and 5.2% (6) had SCARs. In previous studies, patients who used carbamazepine were reported to experience a mild maculopapular rash up to 10%, which is in accordance with our results.<sup>17,18</sup> Although the incidence of DRESS syndrome was reported as 1 in 5000 and the incidence of SJS/TEN as 1 to 6 in 10,000 in adult studies,<sup>19,20</sup> we observed that the rate of carbamazepine-associated SCARs was remarkably higher in children.

In our study, the suspected drug was phenobarbital in 22.6% (7) of patients and all used it as a single drug. In 9.6% (9 of 94) of patients who received phenobarbital, 8.5% (8) had mild cutaneous drug reactions and 1% (1) had DRESS syndrome. Alvestad et al<sup>14</sup> reported that 2% (4 of 211) of patients who used phenobarbital developed a skin rash, but no phenobarbital-associated SCARs were detected. In our study, the rate of phenobarbital-associated cutaneous reactions was higher than in adult studies.

Although the frequency of phenytoin hypersensitivity is reported to be up to 20% in the literature,<sup>2-4,14</sup> there was only 1 patient who developed a rash in our study. Previous studies showed that in the pediatric age group, the risk of mild cutaneous reactions associated with lamotrigine was higher than in adults, but that of lamotrigine-associated SCARs was higher in adults.<sup>21,22</sup> In our study, only 1 of 6 patients using valproic acid developed SJS 10 days after the addition of lamotrigine to treatment with valproic acid and topiramate.

Although aromatic AEDs are more commonly responsible for AED-H, nonaromatic AEDs can cause hypersensitivity reactions rarely.<sup>2-4</sup> Valproic acid, which is a nonaromatic AED, was the most commonly used AED in our study (20%, 285 of 570). The rate of mild cutaneous drug reactions and the rate of SCARs were 4.2% and 3.5%, respectively. Alvestad et al<sup>14</sup> reported that only 1 of 391 patients (0.3%) who used valproic acid developed a maculopapular rash. Therefore, the rate of mild cutaneous reactions and the rate of SCARs associated with valproic acid were observed to be higher than those reported in the literature. Valproic acid is a notable inhibitor of drug metabolism. Inhibition of CYP isoenzymes causes increased plasma phenobarbital concentrations, and inhibition of the UGT1A4 enzyme causes increased lamotrigine levels.<sup>23</sup> Valproic acid also inhibits phenytoin metabolism, causing an increase in the plasma concentration of free phenytoin. Valproic acid can also increase the concentration of the active metabolite carbamazepine-10,11-epoxide through inhibition of epoxide hydrolase, without any substantial changes in the concentration of the parent drug.<sup>23</sup> Studies have indicated that using AEDs in conjunction with valproic acid may increase the risk of AED-H.<sup>23</sup> In accordance with this information, patients who used valproic acid as monotherapy had only mild cutaneous drug reactions, whereas 5 of 18 patients who were using valproic acid with other AEDs experienced SCARs in our study. It is notable that 7 (77.8%) of 9 patients who developed

drug hypersensitivity during multiple AED use were taking a treatment that included valproic acid. These data suggest that patients treated with multiple AEDs containing valproic acid should be monitored more carefully.

Another nonaromatic AED, levetiracetam, is considered to be safe because it has little or no interaction with other AEDs. The rate of this drug's binding to proteins or being metabolized by the P450 enzyme system is negligible.<sup>24,25</sup> A mild cutaneous reaction developed in only 1 of 69 patients treated with levetiracetam in our study. This patient was also taking phenobarbital when levetiracetam was started.

A high starting dose and rapid dose escalation were identified as risk factors, especially for lamotrigine, and particularly when administered concurrently with valproic acid. The risk of allergic reactions is decreased when treatment is started at a low dose and is increased gradually, possibly because slow titration may allow desensitization. A relation between starting dose (and titration rate) and the incidence of cutaneous reactions is particularly evident for lamotrigine, carbamazepine, and phenytoin.<sup>2,3,6</sup> In our study, the AED starting dose was determined according to the child's weight and was the most effective and the lowest dose. The dose was increased slowly until reaching the targeted maintenance dose and effective plasma level.

Several genetic factors that cause a predisposition to SCARs have been previously reported (eg, metabolic enzyme mutations or specific HLA-A, -B, or -C alleles).<sup>2,3</sup> Chung et al<sup>26</sup> first reported a strong association of HLA-B\*15:02 in Han Chinese patients in Taiwan with carbamazepine-induced SJS/TEN, further confirmed by other extended cohorts of this population.<sup>27</sup> An association has been identified between HLA-A\*31:01 and carbamazepine-induced SJS/TEN in predominantly European populations, confirmed also among children.<sup>28-30</sup> A recent study suggested that HLA-B\*15:02 represents a biomarker to carbamazepine-induced SJS-TEN, whereas HLA-A\*31:01 is related to carbamazepine-induced maculopapular exanthema and DRESS syndrome. In addition to HLA types, specific drug-metabolizing phenotypes have been related to AED-H, such as poor metabolizing genotypes of CYP2C9\*3 and phenytoin-associated SCARs.<sup>23</sup> Unfortunately, we could not evaluate HLA alleles of our patients and there are no data collected from our country. Thus, we could not report data regarding relationships to genetic factors.

Data on the role of patch testing in AED-H among children are limited. In our study, patch tests were performed on the patients who gave informed consent. Of 39 AED patch tests on 29 patients, results for 58.6% (17) were positive. In an adult study, Galindo et al<sup>31</sup> showed that the positive predictive value of patch tests was 75% for carbamazepine, 60% for phenytoin, and 25% for phenobarbital and lamotrigine. However, there are studies reporting that the positive predictive value of patch test for carbamazepine is as high as 84.6%. In our study, patch test results with lamotrigine, carbamazepine, valproic acid, and phenobarbital were positive in 100%, 78.5%, 50%, and 28.5% of the tests, respectively. The patch test results with the other AEDs were negative.

## CONCLUSIONS

According to our results, children who are younger than 12 years, who use multiple AEDs, and who use aromatic AEDs more frequently experience AED-H. Therefore, these patients

should be monitored more carefully for drug reactions including SCARs. Furthermore, nonaromatic AEDs with a relatively lower risk of allergic reactions should be preferred when choosing alternative drugs in patients who develop AED-H.

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