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Antiepileptic Medication-induced Severe Cutaneous Adverse Reactions in Hospitalized Children: A Retrospective Study

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ABSTRACT

There are limited data on severe cutaneous adverse reactions (SCARs) associated with antiepileptic medications. The current study aims to investigate the clinical and epidemiological characteristics of antiepileptic medication-induced SCARs in hospitalized children.

This five-year retrospective study was conducted at Isfahan University of Medical Sciences, Iran. The study included all children with a diagnosis of SCARs secondary to antiepileptic medications as defined by the World Health Organization (WHO). In our study SCARs were categorized into three groups: drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), and a group with symptoms overlapping between maculopapular eruptions (MPE) and DRESS.

Among 259 children with SCARs induced by antiepileptic medications, 199 (76.83%), 42 (16.22%), and 18 (6.95%) had overlapping MPE/DRESS, DRESS, and SJS/TEN, respectively. Phenobarbital was the most common offending drug among SCARs. The multinomial logistic regression model revealed that lymphadenopathy increased DRESS occurrence by 35 times compared to overlapping MPE/DRESS. Girls were at risk of SJS/TEN approximately 6 times more than boys. Age, weight, and mucosal involvement affected hospitalization duration in children with SCARs related to antiepileptic medication.

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There are some similarities and differences in the clinical and epidemiological features of Iranian children suffering from antiepileptic medication-induced SCARs.

Keywords: Adverse drug reactions; Allergy and immunology; Antiepileptic drug; Drug reaction with eosinophilia and systemic symptoms

INTRODUCTION

Delayed-type hypersensitivity reactions (DHRs) include a wide range of reactions from mild maculopapular eruptions (MPEs) to severe cutaneous adverse reactions (SCARs). SCARs consist of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), SJS/TEN overlap syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS), and acute generalized exanthematous pustulosis (AGEP). Although SCARs are rare, they can be serious and even life-threatening in some cases.[1,2] These reactions remain unclear in terms of their pathophysiology. Extensive studies have determined that all types of SCARs are delayed type IV hypersensitivity reactions and T-lymphocytes play an important role in the pathophysiology of SCARs. Environmental factors and genetics also affect SCARs pathophysiology .[3,4]

Despite the lack of definitive histological criteria to diagnose different types of SCARs, clinicopathological characteristics support the diagnosis and differentiation of different types of SCARs.[5] AGEP is characterized by the sudden onset of non-follicular sterile pustules on an erythematous background, accompanied by fever and neutrophilia. DRESS and DIHS are characterized by polymorphous skin lesions, fever, lymphadenopathy, and internal organ involvement. Mucosal involvement is also observed in some cases. It can be associated with hematological manifestations, such as eosinophilia and atypical lymphocytosis. Unlike AGEP, DRESS and DIHS have a delayed onset, prolonged course, and frequent relapse. SJS/TEN are severe conditions that cause extensive epidermal detachment, mucosal involvement, and systemic symptoms. In SJS/TEN multiple organ failures can occur. The difference lies in the extent of skin detachment, with SJS affecting less than 10% of the body surface area (BSA), TEN affecting more than 30%, and SJS-TEN overlap involving 10%-30% of the BSA. For SJS/TEN, DRESS/DIHS, and AEGP, the intervals were 1 to 4 weeks, 2 to 8 weeks, and a few hours/days, respectively.[4,6,7] However, clinicians may encounter cases that fulfill multiple diagnostic criteria for these severe reactions, suggesting a combined form of SCARs.[8] Furthermore, it is conceivable that a patient manifests symptoms aligning with both MPE and DRESS diagnostic criteria. In such instances, these patients exhibit fewer systemic symptoms than typical DRESS cases, yet the severity remains similar.[9]

Antiepileptic medications are a major cause of SCARs among children.[10] SCARs induced by antiepileptic medications can lead to stopping or altering antiepileptic medication regimes in children suffering from seizures.[11,12] Although the association between DHRs and the use of antiepileptic drugs has been studied worldwide, there are limited available clinicoepidemiological data on pediatric patients, especially in Iran. To the best of our knowledge, the present study is one of the few available large-scale investigations on the epidemiology of antiepileptic medication-induced SCARs among Iranian hospitalized children.

MATERIALS AND METHODS

Participants and Study Design

This observational retrospective study was conducted at Imam Hossein Children's Hospital, a pediatric referral hospital affiliated with Isfahan University of Medical Sciences, Iran. The ethical committee of Isfahan University of Medical Sciences approved this study (Ethical code: IR.MUI.MED.REC.1399.471) according to the latest version of the Helsinki Declaration. The medical records of hospitalized children who had been diagnosed with SCARs, from March 2014 to March 2019, were reviewed.

Based on the definition provided by World Health Organization (WHO), SCARs are cutaneous adverse drug reactions (CADRs) resulting in persistent or significant disabilities or life-threatening conditions requiring hospitalization or extending patients' hospital stay.[13] According to the WHO definition children who

received a diagnosis of SCARs after taking antiepileptic medications, by the attending pediatric dermatologist and pediatric immunologist, were included in the study. A sufficient time interval between the first administration of the drug and the onset of the reaction was also considered. To determine the culprit drug, the Naranjo Scale was used as an adverse drug reactions probability scale.[14] In our study, patients were categorized into three sub-groups. The first group includes patients who had symptoms overlapping between MPE and DRESS, while not fulfilling all DRESS diagnostic criteria.[9] We mention this group with overlapping MPE/DRESS in the study. Two other groups are patients with definite diagnosis of DRESS and SJS/TEN. The exclusion criteria for SCARs were as follows: indefinite cases of DHRs, histopathology not in favor of SCARs, and incomplete clinical information.

Data Collection

Patients' files were reviewed to collect data, including demographics (age and gender), hospitalization duration, past medical history, offending antiepileptic drugs, the time interval between drug intake and the onset of the reaction, the duration of the drug administration, the sites of skin involvement, laboratory findings, and patient outcomes.

Statistical Analysis

Statistical analyses were performed with SPSS-26 software. Quantitative and qualitative variables were described with mean ± standard deviation (SD) and number (percentage), respectively. According to the diagnosis, patients were divided into 3 distinct diagnostic groups: overlapping MPE/DRESS, DRESS, and SJS/TEN. The chi-square test was used to compare qualitative variables among the three diagnostic groups. The Kolmogorov-Smirnov test was performed to evaluate the normality of quantitative variables. One-way ANOVA and Kruskal-Wallis tests were used to compare quantitative variables among the three diagnostic groups. To evaluate the relationship between qualitative variables and the hospital stay, Kruskal-Wallis and Mann-Whitney U tests were conducted. Pearson and Spearman's tests were applied to investigate the correlation between quantitative variables and the hospital stay duration. The multinomial logistic regression model was applied to assess the relationship between predictors and diagnostic groups. Additionally, a generalized linear model with a log link and gamma distribution was used to assess the relationship between predictors and duration of hospitalization. In both models, the final reduced models were acquired using the stepwise method.

RESULTS

The study included 259 children who diagnosed with SCARs caused by antiepileptic drugs.

Among the participants, 199 (76.83%), 42 (16.22%), and 18 (6.95%) had overlapping MPE/DRESS, DRESS, and SJS/TEN, respectively. Most of the affected children were boys (60.6%, p=0.136). The mean±SD age of the children was 15.65±9.46 months. The demographic and clinical data of the participants are summarized in Table 1. The majority of children suffered from non-febrile seizures (71.4%). The average hospitalization duration for children with SJS/TEN, DRESS, and overlapping MPE/DRESS was 3.9±2.07, 6.5±4.44, and 8.9±3.66 days, respectively (p=0.001). There was a significant relationship between the DHR type and patients' ages (p=0.001). The incidence of lymphadenopathy in children with DRESS was significantly higher than in other participants (35.7%, p<0.001). All patients with SJS/TEN had mucosal involvement (100%, p<0.001).

The most common culprit drug was phenobarbital (85.7%). The most prevalent type of reaction following phenobarbital consumption was overlapping MPE/DRESS (77.93%). Table 2 shows a detailed distribution of DHRs based on the culprit drugs.

Table 1. Demographic characteristics and clinical findings in overlapping MPE/DRESS, DRESS and SJS/TEN.

Characteristics	overlapping MPE/DRESS N=199	DRESS N=42	SJS/TEN N=18	Total N=259	p^*
Age (month)	39.72±35.16	17.84±10.34	21.04±11.87	15.65±9.46	**0.001**
Temperature	37.42±0.96	38.08±1.16	38.06±0.69	37.58±1.01	**<0.001**
Duration of hospitalization	3.92±2.07	6.48±4.44	8.89±3.66	4.69±3.09	**<0.001**
Sex					
Female	74 (37.2)	17 (40.5)	11 (61.1)	102 (39.4)	0.136
Male	125 (62.8)	25 (59.5)	7 (38.9)	157 (60.6)	
Seizure type					
FC	59 (29.6)	12 (28.6)	3 (16.7)	74 (28.6)	0.506
Non-FC	140 (70.4)	30 (71.4)	15 (83.3)	185(71.4)	
PMH					
None	77 (38.7)	16 (38.1)	10 (55.6)	103 (39.8)	
Genetic epilepsy	100 (50.3)	21 (50)	7 (38.9)	128 (49.4)	0.705
Others	22 (11.1)	5 (11.9)	1 (5.6)	28 (10.8)	
Skin involvement					
Generalized	58 (30.2)	16 (38.1)	8 (44.4)	82 (32.5)	0.328
Non-generalized	134 (69.8)	26 (61.9)	10 (55.6)	170 (67.5)	
Mucosal involvement					
Yes	22 (11.1)	12 (28.6)	18 (100)	52 (20.1)	**<0.001**
No	177 (88.9)	30 (71.4)	0 (0)	207 (79.9)	
Facial erythema					
Yes	5 (2.5)	2 (4.8)	5 (27.8)	12 (4.6)	**<0.001**
No	194 (97.5)	40 (95.2)	13 (72.2)	247 (95.4)	
Lymphadenopathy					
Yes	3 (1.5)	15 (35.7)	1 (5.6)	19 (7.3)	**<0.001**
No	196 (98.5)	27 (64.3)	17 (94.4)	240 (92.7)	
ICU admission					
Yes	1 (0.5)	2 (4.8)	3 (16.7)	6 (2.3)	-
No	198 (99.5)	40 (95.2)	15 (83.3)	253 (97.7)	

Data was presented by number (%) or mean±SD. MPE: Maculopapular Eruptions; DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms; SJS/TEN: Stevens Johnson Syndrome or Toxic Epidermal Necrolysis; FC: Febrile Convulsion; PMH: Past Medical History; ICU: Intensive Care Unit; *: *p*-values of categorical and numerical variables are calculated with chi-square and one way ANOVA tests, respectively.

Table 2. Distribution of drug reactions based on culprit drug in overlapping MPE/DRESS, DRESS, SJS/TEN

Drug	overlapping MPE/DRESS N=199	DRESS N=42	SJS/TEN N=18	Total N=259
Phenobarbital	173 (86.9)	38 (90.5)	11 (61.1)	222 (85.7)
Combination PP	12 (6)	1 (2.4)	2 (11.1)	15 (5.8)
Carbamazepine	7 (3.5)	2 (4.8)	3 (16.7)	12 (4.6)
Lamotrigine	1 (0.5)	0 (0)	0 (0)	1 (0.4)
Lamotrigine + Depakene	1 (0.5)	0 (0)	0 (0)	1 (0.4)
Clonazepam	1 (0.5)	0 (0)	2 (11.1)	3 (1.2)
Topiramate	1 (0.5)	0 (0)	0 (0)	1 (0.4)
Phenytoin	2 (1)	1 (2.4)	0 (0)	3 (1.2)
Ethosuximide	1 (0.5)	0 (0)	0 (0)	1 (0.4)

Data was presented by number (%). MPE: Maculopapular Eruptions; DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms; SJS/TEN: Stevens Johnson Syndrome or Toxic Epidermal Necrolysis

There was a significant relationship between the types of DHRs and the average amount of aspartate aminotransferase (AST) (p=0.003), and alanine transaminase (ALT) (p=0.001). The highest average level of liver enzymes was observed among participants with DRESS (AST=109.86±126.69 U/L, ALT=105.14±126.84 U/L). Moreover, the highest average level of international normalized ratio (INR) was observed among children with DRESS (1.18±0.21, p=0.039). The incidence of atypical lymphocytes was significantly different according to the type of reaction (DRESS: 12 (66.7%), p<0.001).

Table 3 shows the laboratory and clinical predictors of overlapping MPE/DRESS, DRESS, and SJS/TEN using a multinomial logistic regression model. According to the model, each one-degree centigrade increase in body temperature increased the risk of DRESS by 1.97 times compared to overlapping MPE/DRESS (p=0.023). An increase of one unit in AST increased the risk of DRESS by 1.02 times compared to overlapping MPE/DRESS (p=0.028). The presence of lymphadenopathy increased the occurrence of DRESS by 35 times compared to overlapping MPE/DRESS (p<0.001). One unit increase in C-reactive protein (CRP) increased the risk of SJS/TEN by 2.3 times compared to overlapping MPE/DRESS (p=0.045). Females were at risk of SJS/TEN by 5.9 times compared to males (p=0.027).

Table 4 shows the predictors of hospitalization duration using a generalized linear model with log link and gamma distributions. According to the model, mucosal involvement lengthened the hospitalization by 0.45 days or 10.8 hours (p<0.001). Each one-kilogram increase in weight increased the duration of hospitalization by 0.03 days or 43 minutes (p=0.036). Every one-month increase in age lengthened the hospitalization by 0.007 days or 10 minutes (p=0.021).

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Table 3. Relationship between studied predictive factors with diagnostic groups using multinomial logistic regression model

Predictors	*p*	OR	95% CI for OR	
			Lower	Upper
DRESS				
(Ref: overlapping MPE/DRESS)				
Weight	0.152	1.132	0.955	1.341
Age	0.426	0.984	0.947	1.023
Temperature	**0.023**	1.974	1.099	3.543
AST	**0.028**	1.021	1.002	1.041
ALT	0.132	0.985	0.966	1.005
CRP	0.492	1.268	0.644	2.494
Sex				
Female	0.298	2.064	0.528	8.067
Male (Ref.)				
Lymphadenopathy				
Yes	**<0.001**	35.816	6.668	192.384
No (Ref.)				
SJS/TEN				
(Ref: overlapping MPE/DRESS)				
Weight	0.855	0.979	0.781	1.228
Age	0.313	1.024	0.978	1.072
Temperature	0.223	1.543	0.768	3.102
AST	0.480	1.013	0.977	1.052
ALT	0.148	0.968	0.927	1.012
CRP	**0.045**	2.333	1.017	5.351
Sex				
Female	**0.027**	5.927	1.222	28.755
Male (Ref.)				
Lymphadenopathy				
Yes	0.442	2.715	0.213	34.587
No (Ref.)				

OR: Odds ratio; CI: Confidence interval; DRESS=: Drug reaction with eosinophilia and systemic symptoms; Ref.: Reference; MPE: Maculopapular Eruptions; AST: Aspartate aminotransferase (Unit/Liter); ALT: Alanine aminotransferase (U/L); CRP: C-reactive protein; SJS/TEN: Stevens Johnson syndrome or Toxic epidermal necrolysis.

Table 4. Relationship between studied predictive factors and duration of hospitalization in patients using generalized linear model with log link and gamma distribution.

Predictor	*p*	Coefficient regression (β)	95% CI	
			Lower	Upper
Seizure Type				
FC	0.894	0.014	-0.192	0.220
Non-FC (Ref.)				
Lymphadenopathy				
Yes	0.190	0.186	-0.092	0.465
No (Ref.)				
Skin involvement				
Generalized	0.338	0.106	-0.110	0.322
Non-generalized (Ref.)				
Mucosal involvement				
Yes	**<0.001**	0.448	0.220	0.675
No (Ref.)				
Weight	**0.036**	-0.031	-0.060	-0.002
Age	**0.021**	0.007	0.001	0.014
Temperature	0.543	0.033	-0.073	0.138
Eosinophil	0.252	0.012	-0.008	0.032
AST	0.100	0.002	0.000	0.005
ALT	0.279	-0.002	-0.004	0.001
ESR	0.108	0.004	-0.001	0.009
CRP	0.336	0.055	-0.057	0.167
Na	0.598	-0.007	-0.034	0.019

CI: Confidence Interval; FC: Febrile Convulsion; Non-FC: Non-febrile Convulsion; Ref.: Reference; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ESR: Erythrocyte Sedimentation Rate; CRP: C - reactive protein; Na: Sodium ion.

DISCUSSION

Our study demonstrated that most of the affected children were male. The most frequent type of SCAR caused by antiepileptic drugs was overlapping MPE/DRESS followed by DRESS and SJS/TEN. Phenobarbital was the most common culprit drug prescribed for children. Our study showed mucosal involvement was evident in all SJS/TEN. Conversely, only a minority of patients diagnosed with DRESS and overlapping MPE/DRESS exhibited mucosal involvement. Children with DRESS had significantly higher lymphadenopathy incidence than other participants. Hospitalization duration was associated with factors such as age, weight, and mucosal involvement in children with SCARs induced by antiepileptic medications.

In line with our study, Shiohara et al, demonstrated that DRESS occurs more frequently than SJS/TEN in patients experiencing SCARs.[15] According to our results, the most common culprit drug in children diagnosed with DHRs was phenobarbital. Another study by our team showed that phenobarbital was the most frequent cause of SJS/TEN in children with epilepsy.[16]

Similar to previous studies on DHRs,[17] most of the affected children in our study were males. The study by Oh et al. on Korean pediatric patients revealed that about 70% of children with SCARs were boys.[17] Unlike the pediatric population, adult females seem to be more affected by SCARs than males.[18,19] Compared to adult men, females are 6 times more likely to be affected by SJS/TEN. A higher prevalence of SJS/TEN in females has also been reported in other studies with a ratio of 10:6 compared to males.[20,21] A possible explanation for this phenomenon could be the effect of female sex hormones. Estrogen hormone in adult females makes them more susceptible to SCARs by increasing antibody and T-cell lymphocyte production. As mentioned earlier, T-lymphocytes are the main mediators of DHRs.[19]

The results of our study demonstrated that mucosal involvement was significantly more common in children with SJS/TEN. All children with SJS/TEN had mucosal involvement. This finding is in line with previous studies.[22-24] According to a 10-year retrospective study involving 61 children diagnosed with Erythema Multi-Form (EM), SJS, and TEN, it was determined that 61% of the children exhibited mucosal involvement.[23] Moreover, in another study conducted among Asian children diagnosed with SJS/TEN, it was observed that all children had mucosal involvement in a minimum of two mucous membranes.[22] The prevalence of lymphadenopathy was significantly higher in children with DRESS than in other participants. In our study, lymphadenopathy increased the occurrence of DRESS by 35 times compared to overlapping MPE/DRESS. This agrees with the previous studies.[15-19,25,26] According to a French systematic review of 49 pediatric patients with DRESS, lymphadenopathy was the third most common manifestation observed in nearly 70% of cases.[25]

In our study, the highest rate of abnormal peripheral blood smear (PBS) was observed in children with DRESS. Similar to our results, a study among 58 children diagnosed with SCARs demonstrated that abnormal PBS (including eosinophilia and atypical lymphocytes) is more prevalent among children with DRESS compared to the ones diagnosed with other types of SCARs.[27] In a study among 132 patients with CADR, 78.4% of the patients with DRESS exhibited eosinophilia, whereas only 11.8% of the patients with overlapping MPE/DRESS showed eosinophilia.[9] The results of an American study on 130 pediatric cases revealed that lymphadenopathy, elevated liver enzymes, and abnormal PBS (such as peripheral eosinophilia, and atypical lymphocytes) were the clinical characteristics associated with DRESS.[28]

In the present study, each one-unit increase in CRP was associated with an increased risk of SJS/TEN by 2.3 times compared to overlapping MPE/DRESS. This finding is reasonable given the existence of severe acute inflammatory skin reactions in SJS/TEN.[29,30]

Generally, hospitalization duration in children is associated with psychological stress for both parents and children.[31] On the one hand, the mean hospitalization period for children with SJS/TEN and DRESS was significantly longer than for others with overlapping MPE/DRESS. On the other hand, our study shows that mucosal involvement prolongs hospitalization. One possible explanation for the increased hospitalization duration in SJS/TEN can be related to mucosal involvement and associated complications. In agreement with our findings, Bequignon et al. demonstrated that ear, nose, and throat (ENT) symptoms of SJS/TEN (such as dysphagia, dysphonia, shortness of breath, odynophagia, earache, and nasal obstruction) may

become complicated during the course of SJS/TEN, which can lead to longer hospitalization in children.[32]

This study provides up-to-date and complementary information on SCARs in Iranian children taking antiepileptic medications. Although SCARs and DHRs are rare among children, since they can lead to potentially severe and critical courses, identifying the clinicoepidemiological characteristics of children suffering from antiepileptic medication-induced SCARs is crucial. Despite the clinical importance of our study, it has some limitations due to its retrospective nature, in which some records were incomplete or illegible.

In conclusion, there are some similarities and differences in the clinical and epidemiological features of Iranian children suffering from antiepileptic medication-induced SCARs. Given the widespread use of antiepileptic drugs, including phenobarbital, physicians must be aware of the potential side effects of these drugs, especially in pediatric patients. In order to obtain more accurate information regarding the association between antiepileptic medication-induced SCARs and clinicoepidemiological features in the pediatric population, prospective studies are necessary.

STATEMENT OF ETHICS

This manuscript has been approved by the ethical committee of Isfahan University of Medical Sciences with approval ID of: IR.MUI.MED.REC.1399.471 according to the declaration of Helsinki.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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