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Original Article

Dermatology Section

Clinico-Epidemiological Profile and Treatment Outcome of Severe Cutaneous Adverse Drug Reactions in the Paediatric Age Group of 0 to 18 Years: A Retrospective Cohort Study from Southern India

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ABSTRACT

Introduction: The paediatric population is prone to developing cutaneous adverse drug reactions. However, the incidence of Severe Cutaneous Adverse Drug Reactions (SCAR) is rare in this age group, with few studies describing such reactions in detail.

Aim: To describe the clinico-epidemiological factors, drug profile, laboratory parameters, and treatment outcomes of SCAR in children admitted to a tertiary care centre in South India.

Materials and Methods: A retrospective cohort study was carried out over a 10-year period, including paediatric patients (0-18 years) admitted to Dermatology, Medicine, and Paediatric wards in the tertiary care centre. Demographic details, suspected drugs, comorbidities, personal and family history of drug reactions, physical examination, laboratory parameters, treatment received along with its duration, and the state of morbidity and mortality were recorded. SPSS version 18.0 was used for analysis. Descriptive statistics were used to summarise the demographics and clinical characteristics of the patients.

Results: Among all the patients admitted with SCAR, 27 (15%) belonged to the paediatric age group. The median age was 15 years, and the female-to-male ratio was 1.25. Nineteen (70.3%) were diagnosed with Stevens-Johnson Syndrome (SJS)/Toxic Epidermal Necrolysis (TEN), and eight (29.6%) were diagnosed with Drug Reaction with Eosinophilia and Systemic Symptom (DRESS). There were no cases of Acute Generalised Exanthematous Pustulosis (AGEP). The most common class of drugs implicated was antiepileptics (62.8%). Two patients (7%) had a family history of drug reactions. All patients had mucosal involvement. The majority of the children responded to intravenous steroids, and two required additional intravenous immunoglobulin injections for clinical improvement. All cases were cured with no mortality or long-term sequelae.

Conclusion: The incidence of SCAR in the paediatric age group is significant. Anticonvulsants, particularly phenytoin, carbamazepine, and lamotrigine, need to be used with caution in this age group. Prompt diagnosis and treatment with systemic steroids can reduce mortality, morbidity, and long-term sequelae.

Keywords: Drug hypersensitivity syndrome, Stevens-Johnson syndrome, Toxic epidermal necrolysis

INTRODUCTION

Cutaneous adverse drug reactions constitute 35% of all adverse drug reactions in children. However, most of these reactions are benign and subside after the withdrawal of the drug and simple supportive management [1].

The term 'SCAR' denotes a group of drug reaction patterns that encompass SJS, TEN, AGEP, and DRESS [2]. In the paediatric population, it has been observed that the incidence of such severe forms of adverse cutaneous reactions that are potentially life-threatening is far fewer [1]. Research findings show that although the incidence of SCAR in children is rare, long-term sequelae can be serious [3-5].

However, there remains a paucity of data in Indian patients. Additionally, the short- and long-term outcomes of children with SCAR are not well understood, and a better awareness of the current disease management is essential to identify potential opportunities for improved treatment and reduction in complications.

The present study is part of the research project titled "A 10-year retrospective study of adverse cutaneous drug reactions among inpatients in a tertiary care centre." Other publications that were published from data acquired in this research project dealt with drug reactions resulting from Ayurvedic and polyherbal preparations [6,7].

The present study aims to describe the epidemiology, clinical patterns, laboratory investigations, treatment, and outcome of paediatric patients admitted to our tertiary care centre with SCAR.

MATERIALS AND METHODS

This retrospective cohort study is part of the research project titled "A 10-year retrospective study of adverse cutaneous drug reactions among inpatients in a tertiary care centre," approved by the Institutional Ethics Committee (IEC No. 05/25/2014/MCT) of Government Medical College Trivandrum. The study was conducted according to the Declaration of Helsinki and includes data from 506 cases of adverse cutaneous drug reactions from January 2005 to December 2014.

In the presnt study, the authors included the data of paediatric patients aged between 0-18 years who were admitted to the Dermatology, Medicine, and Paediatric wards of the tertiary care centre and diagnosed with SCAR during the study period. The age, sex, suspected drug/drugs, comorbidities, personal and family history of drug reactions, physical examination, laboratory parameters, treatment received along with its duration, and the state of morbidity and mortality were recorded.

DRESS: The diagnosis of DRESS syndrome was evaluated using the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) scoring system [8]. It was based on the presence of mucocutaneous

rash, fever, lymphadenopathy, and haematological anomalies such as eosinophilia, atypical lymphocytes, and internal organ involvement. Using RegiSCAR, patients with a score of under 2 points were diagnosed as "not DRESS," those with a score of 2 to 3 points were diagnosed as "possible DRESS," those with a score of 4 to 5 points were diagnosed as "probable DRESS," and those with a score of more than 5 points were diagnosed as "DRESS."

SJS/TEN: Although, there are no universally accepted criteria, diagnosis is based on cutaneous and mucous membrane manifestations, systemic involvement, and histological findings. The acute onset of mucous membrane involvement (at least 2 mucosal surfaces) and skin symptoms (macules, target-like, bullae, or erosion, positive Nikolsky sign) together with epidermal detachment of less than 10% of the total body surface area are regarded as SJS. Epidermal detachment of more than 30% of the total body surface area together with similar clinical signs is classified as TEN, and epidermal detachment of 10% to 30% is classified as SJS/TEN overlap [9].

AGEP: Diagnosis was made according to criteria suggested by Sidoroff A et al., which include: i) Numerous small (<5 mm), non-follicular pustules arising on a widespread oedematous erythema; ii) Pathology showing intra-epidermal/sub-corneal pustules associated with one or more of the following: dermal oedema, vasculitis, perivascular eosinophils, focal necrosis of keratinocytes; iii) fever >38°C; iv) Blood neutrophil count >7×100/L; and v) Acute progression with spontaneous recovery within 15 days [10].

STATISTICAL ANALYSIS

The SPSS version 18.0 was used for analysis, and descriptive statistics were used to summarise the demographics and clinical characteristics of the patients.

RESULTS

During the 10 year period of the study, there were 179 patients admitted with SCAR, of which only 27 (15%) belonged to the paediatric age group of 0-18 years. The age of the patients ranged between three and 18 years, with a median age of 15 years. The most commonly affected age group was between 13-18 years. There were 15 females and 12 males, with a female-to-male ratio of 1.25 [Table/Fig-1].

Age group [years]	Frequency		Total n (%)
	Male	Female	
0-6	1	0	1 (3.7%)
7-12	0	1	1 (3.7%)
13-18	11	14	25 (92.5%)

[Table/Fig-1]: Age and sex of paediatric SCAR patients.

The most common presenting complaint was pruritic rashes seen in 19 patients (70.3%). Other symptoms included blistering, erosions, and mucosal involvement. The most common class of drugs implicated was antiepileptics. Among them, carbamazepine was the most common drug, closely followed by phenytoin [Table/Fig-2].

	No. of patients in whom the drug was suspected
Antiepileptics	
Carbamazepine	9
Phenytoin	8
Phenobarbitone	2
Lamotrigine	1
Antibiotics	
Amoxycillin	2
Ciprofloxacin	1
Gentamycin	1
NSAIDS	
Paracetamol	2
Mefenamic acid	1
Psychiatric drugs	
Olanzepine	2
Quetiapine	1
Modafinil	1
Others	
Pantoprazole	1
Deriphyllin	1
Ayurvedic preparation	1*

[Table/Fig-2]: Causative drugs in SJS/TEN (n=19) and DRESS (n=8).
*Data included in prior publication by the authors [6]

The most common indication for starting the drug was seizures. In one patient, an Ayurvedic polyherbal preparation was determined to be the causative drug. The authors have included this case in a case series on "Severe cutaneous adverse reactions to Ayurvedic drugs" published elsewhere [6].

Among the comorbidities observed, 11 (40.7%) patients had a history of seizure disorder, three (11.1%) were atopic, four (14.8%) had psychological comorbidities, including mental retardation and behavioural abnormalities, two (7.4%) patients had cardiac conditions (one mitral valve regurgitation and the other tetralogy of Fallot), and one (3.7%) had hypothyroidism. Two (7.4%) patients had a family history of drug reactions.

The characteristics of mucocutaneous involvement and laboratory parameters are represented in [Table/Fig-3]. Among the 27 patients included in the study, 19 (70.3%) patients were diagnosed with SJS/TEN, and 8 (29.6%) were diagnosed with DRESS. There were no cases of AGEP. Among the nineteen diagnosed with SJS/TEN, 6 (22.2%) patients were diagnosed with SJS, 5 (18.5%) patients had SJS-TEN overlap, and 8 (29.6%) patients had TEN.

Characteristics	SJS/TEN n (19)	DRESS n (8)
The time between drug intake and reactions (days) (d), median (IQR)	14 (5-28)	28 (25-37.5)
Cutaneous Findings (%) Maculopapular exanthema	12 (63.1)	7 (87.5)
Bullous exanthema	6 (31.5)	2 (25)
Target like lesion	10 (52.6)	2 (25)
Denuded skin	8 (42.1)	1 (12.5)
Mucosal involvement (%)	19 (100)	8 (100)
Oral+conjunctival	12	5
Oral+genital	4	1
Oral+conjunctival+genital	3	2
Lymphadenopathy	1	2
Laboratory findings haematological abnormalities (%)	15 (78.9)	8 (100)
Leukocytosis	6	2
Leukopaenia	3	1
Eosinophilia	4	5
Thrombocytopaenia	2	-
Abnormalities in liver function tests	10 (52.6)	7 (87.5)
Abnormalities in renal function tests	3 (15.7)	-
Treatment systemic corticosteroid (short-term)	12 (63.1)	3
Systemic steroid (long-term)	5 (26.3)	5
Systemic corticosteroid+IVIG	2	-
Mortality	-	-

[Table/Fig-3]: Demographic, clinical, and laboratory characteristics of patients.
IVIG: intravenous immunoglobulin

The majority of the children, i.e., 15 (55.5%), responded to short-term steroids, 10 (37%) required long-term steroids, and two (7%) required additional intravenous immunoglobulin injections for clinical improvement. All cases were cured with no mortality or long-term sequelae.

DISCUSSION

The incidence and severity of adverse drug reactions encountered in adults cannot be extrapolated to the paediatric age group as the pharmacokinetics and pharmacodynamics vary significantly [11]. Most studies report an increased incidence of adverse drug reactions among children, which are mostly benign and self-limiting.

However, when it comes to SCAR, the incidence is reported to be around 2%-6.7% [12,13]. In the present study, children constituted 15% of SCAR cases, with older children in the age group of 13-18 years recording the highest incidence (92.5%), and only 7.5% representing an age group younger than twelve years. Simon AK et al., also observed that immunologically mediated drug reactions (Type-IV delayed type hypersensitivity) like SCAR are fewer in younger children below 10 years of age due to an immature immune system [14]. A female preponderance was seen in the present study, which agreed with the study by Rieder M, where female sex is mentioned as a risk factor for developing drug reactions [15].

The most common type of SCAR observed was SJS/TEN (70.3%), followed by DRESS (29.6%), with no cases of AGEP. AGEP is reportedly rare in children [16]. In current literature, paediatric patients with AGEP have mainly been described in case reports and a few case series with small numbers. A recent 10-year retrospective review reported only eight cases, putting the incidence of AGEP in the studied paediatric population at approximately 1 per million children per year [17].

Though antibiotics are the drug class associated most frequently with ADRs in children, studies have revealed that in SCAR, aromatic anticonvulsants are implicated as the major causative drug category [18]. An Ayurvedic polyherbal preparation was found to be the causative agent for DRESS in one patient. The same patient also developed significant transaminitis during the course of the disease. The authors have published another article on the systematic review by Patel TK et al., which also includes Ayurvedic preparations as causative drugs causing SJS/TEN [19]. There have also been reports on the occurrence of hepatotoxicity as part of the drug reaction to Ayurvedic drugs [6,20].

Comorbidities associated with an increased risk of SCAR include liver and renal dysfunction [15], but this was not seen in the present series. Family history was positive in two of our patients. Genetic studies have revealed a predisposition to SCAR that is specific to certain drugs as well as to ethnic factors. An example of this is the highly significant association established between carbamazepine-induced TEN and HLA-B*1502 among Han Chinese [21]. Compared to data from previous studies on the adult population, children tend to have a higher frequency of mucosal involvement [18]. In our series, all patients had mucosal lesions. Hepatic involvement in the form of elevated liver enzymes was the most frequent systemic manifestation (62.9%), followed by renal involvement (11.1%) in the form of hyperuricaemia and elevated serum creatinine in our study. A multicentric study by Dibek Misirlioglu E et al., also reported similar systemic involvement among children with SCAR [4].

A systematic review of SJS/TEN in children found that patients treated with supportive care alone had higher mortality and morbidity rates, while those treated with a combination of corticosteroids and IVIG appeared to have a better outcome [5]. In the present study group, all patients received systemic steroids, with two patients requiring systemic corticosteroids plus IVIG. All patients were cured, with no long-term sequelae. Mortality has been reported to be lower in children than in adults, but sequelae like neurological defects, secondary diabetes mellitus, pneumonia, and sepsis are relatively more common [4,22].

Limitation(s)

There are some limitations in the present study, the primary one being its retrospective nature. All patients in our study were objectively diagnosed using standard scoring systems. Skin biopsy and/or patch testing for suspected drugs were not carried out in most patients as parental consent could not be obtained.

CONCLUSION(S)

In conclusion, the incidence of SCAR in the paediatric age group, though rare compared to adults, is significant. Therefore, maintaining a high index of suspicion is crucial in making a rapid diagnosis of SCARs. Anticonvulsants, particularly phenytoin, carbamazepine, and lamotrigine, need to be used with caution in this age group. The study also highlights the higher incidence of mucosal involvement when compared to adults and the morbidity characterised by raised hepatic enzymes, which need to be closely monitored. Prompt diagnosis and treatment with systemic steroids can reduce mortality, morbidity, and long-term sequelae. Special attention needs to be paid to paediatric SCAR, with initiatives to improve our understanding of this spectrum of disorders, including formulating new diagnostic criteria specifically for children and developing appropriate management guidelines through controlled clinical trials.

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