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Survey on Etiology of Stevens-Johnson syndrome and Toxic Epidermal Necrolysis in Pediatric Patients: A Six-Year Study from Iran

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Abstract

Background
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are among the most severe dermatologic reactions to the drugs. Data about SJS and TEN among pediatric population especially in Iran is limited. This study aimed to investigate the clinical and para-clinical characteristics of pediatric patients with SJS/TEN.

Materials and Methods
From 2010 to 2016, all SJS and TEN children from three teaching hospitals in Mashhad-Iran with age less than 15 years were included in the study. Patients' catechistic, history, physical examinations, progress notes, laboratory findings, medical consults, treatments taken and the final outcome were extracted from medical records by researcher. Data were further analyzed by SPSS (version 17.0).

Results
Among 165 records, 48 children (58.3% male; mean age of 9.1 years) were among the SJS and TEN spectrum. Anticonvulsants (50%; including lamotrigine, phenobarbital, phenytoin, carbamazepine, valproate and clobazam) were the most common drugs followed by antibiotics (38.1%; including cefixime, penicillin, azithromycin, co-amoxiclav, cephalexin, co-trimoxazole and ceftriaxone), and analgesics (9.5%; including acetaminophen, ibuprofen and naproxen). Infectious agents were the possible cause of SJS/TEN in two patients. WBC counts, liver function tests, renal and electrolyte tests were significantly different in SJS and TEN groups.

Conclusion
The main suspected medications found in this study were anticonvulsants and antibiotics and the mortality rate was 12.5%. The main suspected medications found in this study were anticonvulsants and antibiotics and the mortality rate was 12.5%.

Key Words: Iran, Pediatrics, Stevens-Johnson syndrome, Toxic epidermal necrosis.

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1- INTRODUCTION

Toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS) are considered as severe adverse cutaneous drug reactions, involving predominantly the skin and mucous membranes (1). SJS is defined as cases with limited areas of epidermal detachment (<10%); while TEN with large areas of detachment (>30%), and overlap category for patients with areas of epidermal detachment between 10 to 30% (2). Although the incidence rate of TEN/SJS is low, 0.4 to 7 cases per million person-years, a high mortality rate of 23 to 34% during six weeks through the 1-year period has been reported. Besides a remarkable incidence of death among 6-week survivors, has made them as significant concerns (3-8).

Moreover, according to the recent studies, around half of the affected pediatric patients suffer long-term complications and around one-fifth of children develop recurrent SJS during the first seven years after the index episode (9). Nevertheless, lots of unanswered questions have remained about the etiology, triggers, risk factors and treatment of SJS/TEN, which is partly due to the rareness of SJS/TEN (3, 10). Previous studies investigated more than 100 types of drugs as possible causes of SJS/TEN in general population (10-13).

A study conducted on less than five hundreds of SJS/TEN cases showed that sulfonamides, anticonvulsant agents, and allopurinol were the possible triggers of this condition (11-13); however, approximately 20% of TEN/SJS cases are considered as not drug-related (14). Non-medication factors such as HIV (15), herpes virus or Mycoplasma pneumonia (16, 17), radiotherapy (18), lupus erythematosus and collagen vascular diseases(19, 20) have also been hypothesized to increase the risk of SJS/TEN. Multiple studies have been reported in different age groups including children, infants, and newborns, worldwide. However, there are limited numbers of studies which individually assess medication risk factors in children. Moreover, data on pediatric population of Iran diagnosed with SJS/TEN is scarce. This study aimed to investigate the clinical and para-clinical characteristics of pediatric patients with SJS/TEN.

2- MATERIALS AND METHODS

2-1. Study design and setting

This multi-centric retrospective chart review study was conducted on medical records of pediatric patients with SJS/TEN admitted to the pediatric departments of main teaching hospitals of Mashhad University of Medical Sciences (Iran) including Imam Reza, Ghaem and Sheikh Hospitals between January 2010 and September 2016. Census method was used for sampling and all available cases were included.

2-2. Inclusion and Exclusion criteria

Inclusion criteria were age younger than 15 years, and final diagnosis of SJS or TEN. Incomplete records were excluded.

2-3. Data collection

Medical records with ICD-9 codes of L51.1, L51.2, L51.9 and T88.7 [for diagnoses of SJS, TEN, and erythema multiforme (EM), and drug complications, respectively] were reviewed. Data were recorded within a checklist contained six different sections: 1) baseline characteristics including gender, age, initial and final diagnosis; 2) medical history including type and duration of the medications used before the onset of initial symptoms, duration of clinical symptoms, and patient's underlying conditions; 3) physical examination findings such as vital signs at the time of admission, dermatologic description of lesions (i.e. macular, maculopapular, papulovesicular, etc.), level of mucosal involvements (Periorbital infections, perioral, genitalia,

urethral), presence of Nikolsky sign; 4) laboratory findings, including complete blood test, prothrombin time, International Normalized Ratio (INR), blood glucose, albumin, bicarbonate, sodium and potassium, C-reactive protein (CRP), liver enzymes, urea and creatinine, and urine analysis (UA); 5) medical management including treatment ordered (i.e. antibiotics (topical or systemic), intravenous immunoglobulin (IVIg) or corticosteroids, the frequency of required counseling with other specialists, the need for Intensive Care Unit admission and intubation or cardiopulmonary resuscitation; and 6) patient status during hospitalization and final condition during discharge.Moreover, SCORTEN scale (Score of TEN) was calculated if serum bicarbonate, blood urea nitrogen (BUN), and glucose, as well as age, heart rate, presence or absence of underlying malignancy, and percentage of detached or compromised body surface area, were available.

SCORTEN score is a specific severity-of-illness score for cases of SJS and TEN that can predict mortality among these patients. One point is scored for each of seven criteria present at the time of admission which are: 1- age > 40 years, 2- presence of malignancy, 3- heart rate >120, 4- initial percentage of epidermal detachment >10%, 5- serum blood urea nitrogen (BUN) level >28 mg/dL, 6- serum glucose level >252 mg/dL, 7- serum bicarbonate level < 20 mEq/L.

2-4. Ethics

The proposal of this study was approved by the Ethics Committee of the Vice Chancellor for Research at the Mashhad University of Medical, Iran. Also, we were committed to keeping all of the participants' information confidential.

2-5. Statistical analysis

Categorical variables were reported in frequency and percentage, and quantitative information was reported as a mean and standard deviation. Chi-square and independent-sample t-test, were used for comparing different factors between two groups of TEN and SJS with the SPSS Statistics for Windows (Released 2008, Version 17.0. Chicago: SPSS Inc.). Two-tail value of $p < 0.05$ was considered as statistically significant. Also, before performing the statistical analyses, the normality of the variables' distribution was examined using the K-S test.

3- RESULTS

3-1. Baseline Characteristics

Forty eight children (28 males, 20 females) with the diagnosis of SJS (n=31), TEN (n=15), SJS-TEN overlap (n=2), during 2010 and 2016 were included in the study. Mean age was 9.1±0.65 and ranged between 1 and 15 years old.

3-2. SJS progression to SJS/TEN or TEN

Four SJS patients progressed to TEN during the time of hospitalization and then were included in TEN categories. Also, one of the SJS-TEN overlaps had positive Nicolsky's sign but after consulting the dermatologist, the patient was considered as a case of SJS.

3-3. Medical history

Of the 48 patients studied 18 (37.5%) had no underlying conditions and six patients (12.5%) had two underlying conditions. The most common underlying diseases were epilepsy and seizure which were reported in 21 patients (58.3%). It should be noted that febrile convulsions, afebrile convulsions, and various epileptic syndromes were also included in this group. Apart from brain tumor and depression which were recorded in two patients, other underlying conditions including cerebral palsy, mental retardation, Huntington's disease, autism, obsessive-compulsive disorder, bipolar disorder, Tetralogy of Fallot (TOF),

asthma, cataract, hypothyroidism, and chronic abdominal pain were only reported in one patient. The most common possible trigger for the SJS/TEN was recorded as drug-induced in 46 patients (95.8%). The mean interval from medication use to the first prodromal dermatologic symptoms was 11.8 ± 8.5 days, ranged between 1 to 38 days. The suspected medications to cause SJS and TEN were mainly anti-epileptic drug (50%). There were usually multiple culprit drugs used simultaneously for the patient (ranged from 1 to 5 drugs). After reviewing patients' records, 31 different medications were attributed to cause SJS or TEN which were mainly anti-seizures, antibiotics, and sedatives (**Table.1**). Two other possible triggers were recorded as infection (n=1), probably due to Mycobacterium, and pneumonia which was exacerbated after taking azithromycin (n=1). Also, the cause of the disease remained unknown in one of the cases.

Table-1: List of culprit drugs used for the pediatric patients with Stevens - Johnson syndrome and Toxic Epidermal Necrolysis

	Anti-seizures (50%)						Antibiotics (38.1%)								Sedatives (9.5%)			Other (2.4%)	
	Lamotrigine	Phenobarbital	Phenytoin	Carbamazepine	Valproate	Clonazepam	Cefixime	Penicillin	Azithromycin	Co-amoxiclav	Amoxicillin	Cephalexin	Co-trimoxazole	Ceftriaxone	Acetaminophen	Ibuprofen	Naproxen	Risperidone	Clonidine
Number	13	11	6	6	5	1	8	6	5	4	3	3	2	1	5	2	1	1	1
Percent	15.5	13.1	7.1	7.1	5.9	1.2	9.5	7.1	5.9	4.7	3.6	3.6	2.4	1.2	5.9	2.4	1.2	1.2	1.2

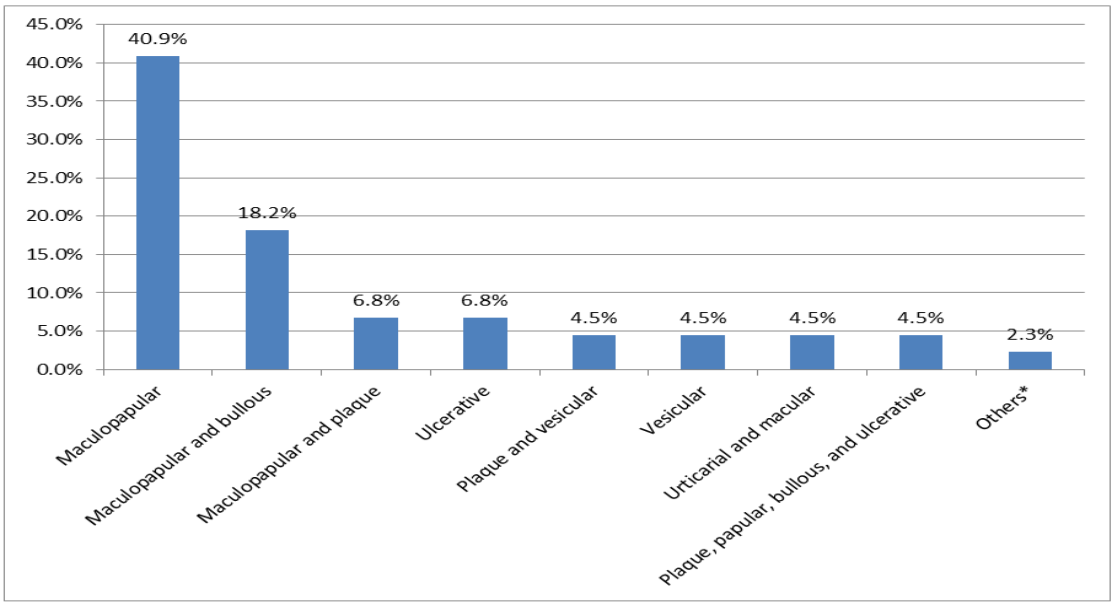
3-4. Physical examinations

3-4-1. Vital signs

The mean temperature was 38.16±0.94 and 38.13±1.13 ċ in SJS and TEN patients, respectively with no significant difference between two groups (p=0.925). Mean pulse rate was 113±20.22 (80-170 beat/min) in SJS and 114.2±15.75 (81-140 beat/min) in TEN patients with no significant difference between two groups (p=0.765).

3-4-2. Lesions characteristics

The most common type of lesion was maculopapular (n=18, 40.9%) (**Figure.1**), and the most common mucosal involvement occurred in perioral and periorbital mucosa (n=16, 34%) (**Figure.2**); the mucosal involvement was not stated for one patient and five patients did not have any mucosal involvement. Also, Nicolsky's sign was positive in 7-patients (14.6%).



*including urticarial, bullous, macular, plaque, and vesicular.

Fig.1: The prevalence of types of skin lesions in pediatric patients with Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis.

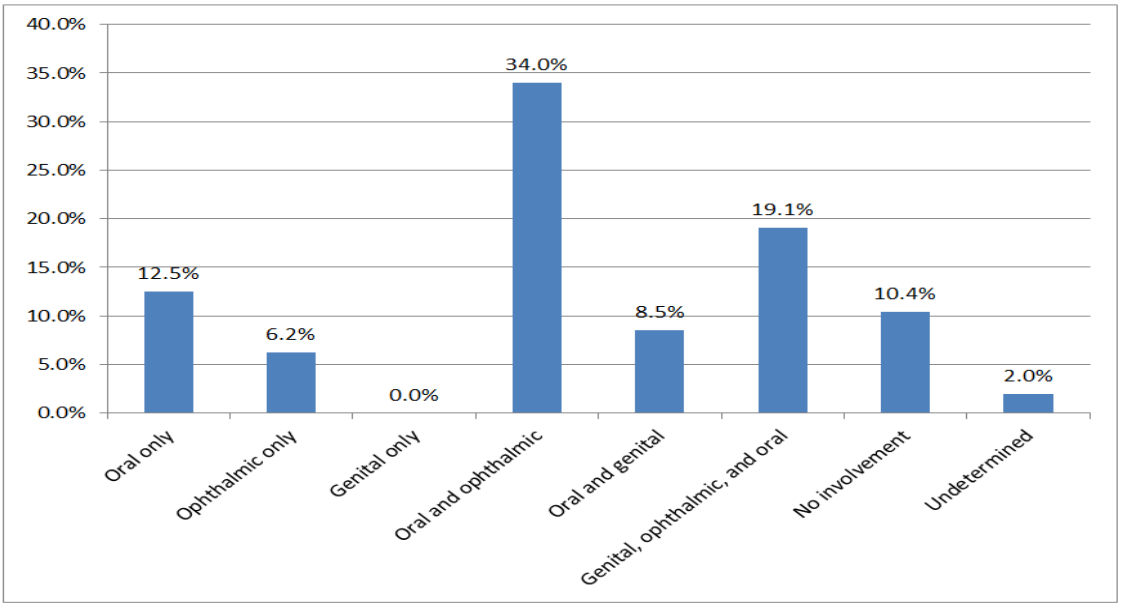


Fig.2: The prevalence of mucosal involvement in pediatric patients with Stevens-Johnson syndrome and Toxic Epidermal Necrolysis.

3-5. Laboratory parameters

Laboratory findings are shown in (**Table.2**). The prothrombin time (PT) and international normalized ratio (INR) were reported normal in 15 of 25 patients (60.0%). Moreover, 23 of 31 patients (74.2%) had normal UA, while 19.4% had pyuria, 3.2% had hematuria, and 3.2% had concurrent hematuria and glycosuria. Also, C-reactive protein (CRP) was negative in 4 of 30 patients (13.3%). The microbial culture was conducted for 5 cases of these patients which were positive in 4 cases (Two had positive urine culture, one had a

positive ulcer and urine culture, and one had positive blood and ulcer culture).

3-6. Treatment procedures

Dermatologic and ophthalmologic consult was asked for 35 (79.5%) and 34 (77.2%) cases, respectively. Fourteen patients received supportive treatments such as wound dressing, serum therapy, Nutritional counseling, etc. One of these patients suffered from TEN. Other patients received at least one supportive treatment (IVIg, corticosteroid, or both) (**Table.3**). Some patients received multiple systemic antibiotics for treatment (ranged between 0-6 drugs with an average of 1.77). Also, the average of topical antibiotic usage was 1.55 and ranged between 0 and 4. Twelve patients were hospitalized in intensive care unit (ICU) during their hospitalization; eight of them were diagnosed with TEN cases, and two had SJS. Also, two of the admitted patients in ICU were diagnosed with SJS-TEN overlap.

3-7. Patients status

Two patients self-discharged themselves, and six died in hospital, in which four of them were in the ICU and three of them suffered from TEN. The mean hospitalization period was 7.54±3.614 and 11.86±5.231 in SJS and TEN patients, respectively (p=0.004). Also, mean hospitalization period was 11.7 days in deceased patients.

3-8. SCORTEN scale

SCORTEN was available for 13 patients and ranged between 0 and 4 with an average of 2.4. Four of these patients had bicarbonate below 20 (30%), eight had urea above 28 (61%), one had glucose above 252 (7%), eight had total body surface area (TBSA) more than 10% (61%), nine had heart rate>120/min (69%), and none of them had malignancy.

3-9. TEN and SJS comparison

Frequency of ICU admission and the need for IVIg were significantly higher in TEN patients compared to SJS (p=0.001 for both). Duration of hospitalization, the total number of consultations, white blood cell (WBC) count, potassium, liver injury enzymes and creatinine levels were also significantly higher in TEN patients compared to SJS. Other factors were not significantly different between two groups.

Table-2: The comparison of Laboratory findings between SJS and TEN patients.

Variables	SJS	TEN	P-value
	Mean ± SD	Mean ± SD	
Glucose (mg/dL)	109.70± 44.09	116.93± 36.831	0.611
Urea (mg/dL)	25.707 ±11.409	36.160± 26.845	0.083
Creatinine (mg/dL)	0.638± 0.158	0.793± 0.194	0.009
WBC count (/mm^3)	9705± 3221.9	7150± 3315.2	0.021
Hemoglobin (g/dL)	11.879± 1.3461	11.414± 1.286	0.291
Platelet count(/mm^3)	310.04±127.620	267.07± 126.368	0.308
Sodium (mEq/L)	136.82± 4.234	135.71± 2.585	0.376
Potassium (mEq/L)	4.186± 0.579	4.643± 0.637	0.025
Bicarbonate (mEq/L)	96.769±17.95	9.329±12.57	0.123
ALT(Unit/L)	29.17± 19.00	102.75± 134.086	0.028
AST(Unit/L)	30.89± 30.6	85.83± 83.89	0.001
ESR(mm/h)	26.222± 18.851	45.308± 34.637	0.058
Albumin (g/dL)	3.867± 0.666	2.875± 0.704	0.118

TEN: Toxic epidermal necrolysis; SJS: Stevens–Johnson syndrome; SD: Standard deviation; WBC: White blood cell; ALT: Alanine Aminotransferase; AST: Aspartate transaminase.

Table-3: Treatment procedures for SJS and TEN patients

The Supportive treatment for SJS TEN patients				
Intravenous immunoglobulin		IV Ig Number (%)		Total
		Yes	No	
Corticosteroid	Yes	11 (35.5)	20 (64.5)	31
	No	3 (17.7)	14 (82.3)	17
Total		14 (29.2)	34 (70.8)	48

IV Ig: Intravenous immunoglobulin; TEN: Toxic epidermal necrolysis; SJS: Stevens–Johnson syndrome.

4- DISCUSSION

In this study, the possible triggers of SJS/TEN in three referral hospitals in North East of Iran were investigated. Unfortunately, due to the infrequent nature of the disease, and also choosing the subgroup of children for study, conducting prospective studies seemed almost impossible. Despite the acceptance of this shortcoming, the present multi-centered study was designed and conducted in cooperation with the medical records unit of three hospitals. This study was conducted in a 6-year period, and 48 patients were admitted with SJS, TEN and SJS-TEN overlap diagnoses in this interval. This number was predictable assuming a population of 3 million and an incidence of 2.5 to 3 people per million. Although, the actual number is likely to be higher than, this since SJS and TEN patients have not solely referred to these three educational centers in Mashhad during the mentioned period. In this study, about half of the hospitalized patients were not resident in Mashhad. The referral of patients from other cities and sometimes adjacent provinces was expected due to Imam Reza Hospital being the largest burn center in the east of the country. In the present study, the male to female ratio was 1.4. Other studies show relatively higher incidence of SJS or TEN among males (7, 9). The reason is not well known but seems to be geographically dependent. The Food and Drug Administration (FDA) report, the largest sample ever published in the pediatric subgroup, also had partial male gender predominance (21). More than half of the patients in this study used more than one suspected drug in their history. The use of multiple drugs theoretically can increase the risk of death in SJS and TEN patients. In this study, one of three patients who used five suspected drugs simultaneously died. The average number of drugs used in the deceased group was 2.33 and 1.66 in the recovered group. As far as the authors are concerned, no study has been done to examine this variable, but the fact that taking multiple drugs in the pediatric population is more common has been previously addressedin the literature (22). In many studies in the pediatric age group, there are cases where no specific etiology is found for the patient. The prevalence of these cases varies between 5% and 25% in various studies. In this study, for 2% of patients, no specific etiology was found. In two of the patients (5.1%), there was an infectious cause, but unfortunately, no specific serology was available to either confirm or reject this possibility. The main suspected drugs in this study were primarily anticonvulsants and secondarily antibiotics. In most previous studies, these two causes are often ranked first and second. Although, antibiotics such as Co-trimoxazole and amoxicillin have been reported as a causative agent in previous studies, but in this study, Cephalosporins

were ranked first that could be due to the extensive prescription of this drug by physicians in this area. Surprisingly, in our study about 30% of suspected drugs were not included in the list of high risk drugs which cause SJS or TEN, and there are only case reports available for them. Unfortunately, in the present study, it cannot be precisely determined whether the mentioned cases were definitely related to the suspected drug. Previously, ALDEN algorithm (an Algorithm for Assessment of Drug Causality in Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis) was developed to determine the possibility that the culprit drug is the real causative agent for SJS or TEN but this algorithm was not used in our study due to retrospective nature of the study and incomplete medical history for the majority of patients. Nevertheless, we partially tried to use the criteria of this algorithm to identify the suspected drug (s) as far as possible (14, 23).

In studies conducted in pediatrics, it has often been mentioned that there is no specific risk factor in the pediatric population causing TEN and SJS. In this study most of our patients (62.5%) had at least one underlying condition, which in most cases were epilepsy and seizure syndromes. There is controversy among researchers as to whether the underlying disease of a patient is also an additional risk factor for development of SJS and TEN or not. For example, some people think of hematologic cancers as a risk factor for TEN and SJS; while other cancers (such as central nervous system cancers) are only considered as the underlying condition for receiving a suspected drug (for example, an anti-seizure medication). Since the present study was not designed as case-control, we could only consider the mentioned diseases as an underlying disease. Epilepsy, psychiatric disorders, malignancy, and asthma were commonly diagnosed in SJS and TEN patients in a study by Finkelstein et al., which was also confirmed in our study (9, 23). In our study, the mortality rate was 12.5%, which is more than previous studies. In two cases, the cause of death was unrelated to the patient's current disease (i.e. SJS and TEN), but even after exclusion of these two cases, the mortality rate in the study would reach 8.3%, which is still high. On the other hand, no consult records were available for some patients in this study, while it is well-known that management of these patients involves different expertise and specialties. SJS can progress to TEN, which was reported in 4 patients. For this reason, some SJS patients may become TEN-approved later in the course of disease (9). The present study was conducted for the first time in a multi-centered population of Iranian pediatric population and is comparable with some international studies regarding sample size.

Nevertheless, the shortcomings of the present study must be addressed. First, the study is a retrospective review of patients' medical records that contain incomplete and sometimes contradictory information. Second, a follow-up study for complete history to investigate the ALDEN algorithm was not performed. Third, SCORTEN was not available for many patients. Fourth, many of the acute complications were not mentioned in the medical records. For example, it was possible to detect urinary tract involvement in the natural course of SJS orTEN, only if there was a history of dysuria in the patient or in cases where urologic consult was available. Fifth, some variables did not come to the researcher's mind at the beginning of this study, among such as description on the type of target lesions (typical or atypical) and how the lesions spread in one or more body surfaces. The most prominent obstacle in SCORTEN calculation for SJS and TEN patients in this study was the absence of

bicarbonate measurement for the majority of patient. Perhaps writing a statement "Perform bicarbonate test on the first and third day of hospitalization to calculate SCORTEN score" in dermatology counseling is not only helpful in making decisions making, but also in training other members of the therapeutic team (such as internist, infectious diseases and pediatric specialists). It is hoped that in the future, this order will be added to the dermatologist's instructions during the consultation.

4-1. Limitations of the study

This retrospective study was conducted on medical records which were in some cases incomplete and there was no access to patients for further supplementary data which was the major limitation in this study.

5- CONCLUSION

This study reinforces that the main suspected medications were anticonvulsants and antibiotics which were consistent with previous studies. The mortality rate in this study was 12.5% which indicates the importance of identifying the etiology. Further studies, such as Human Leukocyte Antigen (HLA) testing in these patients, are now possible, which is recommended for future studies.

6- CONFLICT OF INTEREST: None.

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