



Evaluation of the patients diagnosed with Stevens Johnson syndrome and toxic epidermal necrolysis: a single center experience

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Abstract

Aim: Stevens Johnson syndrome and toxic epidermal necrolysis are severe acute mucocutaneous diseases. In this study, we evaluated the clinical aspects of Steven Johnson syndrome, toxic epidermal necrolysis and Stevens-Johnson syndrome/toxic epidermal necrolysis overlap patients who admitted to our clinics in the last five years.

Material and Methods: Eleven patients diagnosed as Stevens-Johnson syndrome, toxic epidermal necrolysis and Stevens-Johnson syndrome/toxic epidermal necrolysis overlap in Department of Pediatric Allergy in Uludağ University School of Medicine were included in this study. Clinical findings, laboratory tests and response to treatments were evaluated via electronic files.

Results: Two of the patients had Stevens-Johnson syndrome, four had Stevens-Johnson syndrome/toxic epidermal necrolysis overlap, and five had toxic epidermal necrolysis. The median period for drug usage was 10 days (2-44 days). Herpes simpleks virus IgM antibody was detected two patients. The median healing time was 38 days (26-94 days). Maculopapular eruptions and oral mucositis were seen in all patients. Vesicul or bullae, epidermal detachment and ocular involvement in 10 of patients. Wound care, H1 antihistamine and methyl prednisolon were used in all patients, intravenous immunoglobulin were used in 7 patients and cyclosporine in 1 patient. Sequel lesions developed in 2 of the patients and there was no death.

Conclusion: Anticonvulsants, antibiotics and non steroid anti-inflammatory drugs play a major role in the etiology of Stevens-Johnson syndrome and toxic epidermal necrolysis. Anticonvulsants are associated with severe disease. The patients with proper wound care and treatment with immunosuppressive drugs can be recovered without or with minimal sequelae. (Turk Pediatri Ars 2016; 51: 152-8)

Keywords: Child, Stevens Johnson syndrome, toxic epidermal necrolysis

Introduction

Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are life-threatening, delayed type hypersensitivity reactions (1). The estimated mortality rate has been reported to be 1-5% for SJS and 25-30% for TEN (2). Although there is substantial overlapping in terms of clinical, radiological and histopathological findings, the main differentiation point between these two diseases is the area of epidermal separation on the body surface (2, 3). Epidermal separation is observed in less than 10% of the body surface in SJS, in more than 30% of the body surface in TEN and in 10-30% of the body surface in SJS/TEN overlap (3, 4).

The prevalence of Stevens Johnson syndrome and TEN have been reported to be $1,2-6 \times 10^6$ and $0,4-1,2 \times 10^6$ re-

spectively (5, 6). Although the disease occurs in all age groups, it is observed more commonly and has a more severe course in adults (2, 7). In Stevens Johnson syndrome and TEN, cutaneous and mucosal involvement occur following the prodromal period during which nonspecific complaints are observed (2, 7). The second period during which epidermal separation occurs and vesicles and bullae are formed follows the early stage of the disease which is characterized by red-purple maculopapular eruptions (1). Inflammatory changes including purulent conjunctivitis, erosion, ulcer and crusts may be observed in the eye, mouth, nose, pharynx, esophagus, trachea, gastrointestinal tract, urinary tract and genital mucosae (1, 2, 8). Life-threatening bleeding and infections may be observed as a result of these changes (8). The rates of severe complications or sequelae secondary to Stevens-Johnson syndrome and

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TEN are higher in patients with mucosal and ophthalmic involvement (2).

Although it is thought that drug-related type IV hypersensitivity reaction is involved in development of the disease, the pathogenesis has not been elucidated fully (2, 8). As a result of induction of the immune system by drugs which bind to MHC I molecules and T cell receptors, T cells are proliferated clonally and kill keratinocytes directly or indirectly by causing secretion of various cytokines from the other cells (2, 9). Keratinocyte apoptosis may involve all layers of the epidermis and lead to formation of bulla by affecting the subepidermal tissue (2). The other factors which are involved in the pathogenesis of Stevens-Johnson syndrome and TEN include defect in the mechanism of drug bioactivation, low N-acetylation capacity and presence of certain HLA groups (1, 2, 10).

In this study, it was aimed to evaluate the clinical properties, etiologic factors, laboratory data, therapies used and treatment responses in the patients who were followed up with a diagnosis of SJS, TEN and SJS/TEN overlap in the last 5 years in our clinic.

Material and Methods

Eleven patients diagnosed with SJS, TEN or SJS/TEN overlap in Uludağ University School of Medicine, Pediatric Allergy Clinic between 2010 and 2015 were included in the study. The electronic files of the patients were examined retrospectively and the etiologic factors, physical examination findings, laboratory results, therapies used and treatment responses were evaluated. Informed consent was obtained from the patients and ethics committee approval was obtained from Uludağ University School of Medicine, Clinical Researches Ethics Committee (date: 12-22-2015, number: 2015-22/20).

Results

The median age at presentation was found to be 4 years (2,3-17 years). 54.5% of the patients were female (n=6) and 45.4% (n=5) were male. Two patients had been diagnosed with SJS, 4 patients had been diagnosed with TEN and 5 patients had been diagnosed with JS/TEN overlap. The median period of drug usage before presentation was 10 days (2-44 days). The median time for recovery of the lesions was 38 days (26-94 days). The median period of hospitalization was 14 days (6-80 days). While maculopapular eruptions, mucositis

in the mouth and eye involvement were observed in all patients, formation of vesicle and/or bulla and epidermal separation were present in 10 patients (Figure 1). Vacuolization, keratinocyte injury and apoptosis were observed in the basal layer of the epidermis on pathological examination in the patient whose physical examination did not reveal epidermal separation. The maculopapular lesions were extended to the face, trunk, arms and legs in all patients. Wound care, first generation antihistaminic drugs and methyl prednisolone (at a dose of 0.5-2 mg/kg/day for 6-30 days) were used in all patients. Intravenous immunoglobulin (IVIG) was used in seven patients and cyclosporine was used in one patient. Systemic antibiotic treatment was given to five patients and antifungal treatment and antiviral treatment was given to two patients. The drugs which were thought to be etiologic factors for development of the disease, diagnoses, drugs used in treatment and general properties of the patients are shown in Table 1. Herpes simplex virus-specific immunoglobulin M (HSV-IgM) was found to be positive in two patients. The serologic examinations performed by "Enzyme-Linked Immunosorbent Assay" (ELISA) method showed that the other viruses (hepatitis A virus, hepatitis B virus, hepatitis C virus, cytomegalovirus, epstein barr virus, rubella, varicella and parvovirus) and *Mycoplasma pneumoniae* IgM were negative. When the laboratory data were examined, it was found that two patients had lymphopenia (<2 000 /mm³), three patients had anemia (<12 g/dL), five patients had slightly increased alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) level (>40 U/L, <100U/L), seven patients had increased C-reactive protein (CRP) level (>0.5 mg/dL), two patients had slightly decreased sodium level (130-135 mEq/L) and decreased potassium level (<3.5 mEq/L), three patients had decreased albumin level (<3.5 gr/dL) and one patient had hypogammaglobulinemia at the time of presentation. *Pseudomonas aeruginosa* was grown in both cultures in one of five patients in whom hemoculture and skin swab culture were obtained. No growth occurred in the other patients. The laboratory data of the patients are summarized in Table 2. Sequela changes in the form of cutaneous scar and hyperpigmentation were observed in two patients, whereas the other patients recovered without sequela and no patient was lost (Figure 2).

Discussion

It is known that more than two hundred drugs are related with development of SJS or TEN (4). In many

Table 1. General properties of the patients, drugs which are thought to be involved in the etiology and drugs which are used in treatment

Patient number	Gender	Age	Period of drug usage	Diagnosis	Suspicious drug or drugs	Drug groups used in treatment
1	Male	3	15	SJS/TEN overlap	Lamotrigine, valproic acid	Antihistaminic, systemic corticosteroid, IVIG (1.8 g/kg)
2	Male	8	2	SJS/TEN overlap	Ceftriaxon, cefuroxim	Antihistaminic, systemic corticosteroid, systemic antibiotic, systemic antiviral, IVIG (1.8 g/kg)
3	Female	3	2	TEN	Paracetamol, ibuprofen	Antihistaminic, systemic corticosteroid, IVIG (1.5 g/kg), antibiotic, antifungal
4	Male	15	4	SJS/TEN overlap	Valproic acid, penicillin	Antihistaminic, systemic corticosteroid
5	Male	9	10	SJS/TEN overlap	Amoxycillin/clavulonate claritromycin+ibuprofen	Antihistaminic, systemic corticosteroid, IVIG (1.5 g/kg)
6	Female	2	2	TEN	Cefalexin, ceftriaxon	Antihistaminik, sistemik kortikosteroid, IVIG (1 g/kg)
7	Male	3	10	SJS	Amoxycillin/clavulonate	Antihistaminic, systemic corticosteroid
8	Female	12	30	TEN	Lamotrigine, valproic acid	Antihistaminic, systemic corticosteroid, IVIG (2.5 g/kg), cyclosporine, antibiotic, antifungal albumin, erythrocyte transfusion
9	Male	9	44	TEN	Phenytoin, amoxycillin clavulonate	Antihistaminic, systemic corticosteroid, IVIG (2 g/kg), antibiotic, antifungal
10	Female	4	10	SJS	Herbal mixture*, common cold syrup**	Antihistaminic, systemic corticosteroid
11	Female	2, 3	20	TEN	Lamotrigine, valproic acid	Antihistaminic, systemic corticosteroid, IVIG (2.5 g/kg), albumin

IVIG: intravenous immunoglobulin; SJS: Stevens Johnson syndrome; TEN: toxic epidermal necrolysis Cases of SJS/TEN overlap

*Anasona essence, folium menthae essence, taraxacum essence, raziyane nectar, grapefruit essence

**Paracetamol, guaifenesin, prylamine maleate, phenylephrine

studies involving children, it has been reported that drugs including anticonvulsants (phenobarbital, lamotrigine, carbamazepine, valproic acid etc.), antibiotics (sulfonamides, penicillins, cefalosporins etc.), non-steroid anti-inflammatory drugs (NSAIDs) and acetaminophen carry a risk in terms of development of SJS and TEN (1). It was difficult to specify the responsible drug, because most of the patients were using multiple drugs at the time of presentation in our study. When the drugs which were associated with Stevens Johnson syndrome, TEN and SJS/TEN overlap were examined, it was found that the most common causes in this study included anticonvulsants (n=5, 45.4%) and antibiotics (n=5, 45.4%). A positive history of anticonvulsant usage was frequent (3/5) in the patients who were diagnosed with TEN which is the most severe form among these three clinical pictures having common pathogenesis. This result suggested that the possibility of anticonvulsants to cause a severe picture was higher compared to the other drugs.

While development of Stevens Johnson syndrome and TEN has been mostly associated with drugs, a clear

association with drugs can not be established in the majority of the cases including mainly pediatric cases (2). It is thought that microbial agents including viral infections (*Coxsachie virus, influenza virus, Epstein Barr virus, herpes virus 6 and 7, Cytomegalovirus, parvovirus*), bacterial agents (*Mycoplasma pneumoniae, group A beta hemolytic streptococci*) and *rickettsia* may also lead to development of Stevens-Johnson syndrome and TEN (7, 11). In our study, *Herpes simplex virus*-specific IgM was found to be positive in two of our patients.

Although the initial symptoms related with Stevens Johnson syndrome and TEN generally begin 4-14 days after initiation of medication, this period may sometimes prolong up to 3-6 weeks (12). In our study, the median time between initiation of medication and onset of first symptoms was found to be 10 days (2-44 days) in accordance with the literature data.

It has been reported that the prodromal period during which complaints including malaise, fever, pruritus in the eye and dysphagia are observed generally changes between 1 and 14 days in Stevens Johnson syndrome

Tablo 2. Laboratory tests of the patients with a diagnosis of SJS, TEN and SJS/TEN overlap

	Mean	±SD		Mean	±SD
Leukocytes (/mm ³)	10 072.7	2 900.6	Glucose (mg/dL)	89.7	10.7
Neutrophils (/mm ³)	5 841.8	2 790.0	BUN (mg/dL)	10.7	4.6
Lymphocytes (/mm ³)	3 128.6	1 704.3	Creatinine (mg/dL)	0.5	0.0
Monocytes (/mm ³)	784.1	359.9	Na (mEq/L)	135.3	3.1
Basophils (/mm ³)	100.4	48.9	K (mEq/L)	4.2	0.5
Eosinophils(/mm ³)	255.5	241.9	Cl (mEq/L)	103.4	3.3
Hemoglobin (gr/dL)	12.1	1.1	Albumin (gr/dL)	3.7	0.6
Platelets (/mm ³)	322.6	109.7	Protein (gr/dL)	6.6	0.9
AST (IU/L)	40.9	16.7	LDH (IU/L)	391.7	98.6
ALT (IU/L)	29.1	14.6	IgG (mg/dL)	932.7	372.5
ESR (mm/saat)	3.2	2.7	IgA (mg/dL)	108.3	79.6
CRP (mg/dL)	3.0	3.2	IgM (mg/dL)	119.5	58.9

SJS: Stevens Johnson syndrome; TEN: toxic epidermal necrolysis; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BUN: blood urea nitrogen, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate



Figure 1. Epidermal separation, mucositis, formation of bulla, eye involvement, maculopapular eruptions which tend to confluence and target-like lesions in patients with a diagnosis of SJS/TEN
S: Stevens Johnson syndrome; TEN: toxic epidermal necrolysis

and TEN (2, 7). While pharynx involvement is observed in almost all patients, eye involvement is observed in approximately 80% of the patients (1, 2). In our study, the median prodromal period was found to be 2 days (1-4 days). Fever and mucosal involvement in association with maculopapular eruptions were present in all patients. Maculopapular eruptions were extended in the face, trunk, arms and legs in all patients. Formation of vesicles and/or bulla were present in 10 patients. Eye



Figure 2. Appearance of the patients with a diagnosis of SJS/TEN overlap before and after treatment
SJS: Stevens Johnson syndrome; TEN: toxic epidermal necrolysis

involvement was found in 10 of the patients including severe conjunctivitis in association with pseudomembrane in three patients.

Electrolyte disorders, reduced albumin, hypovolemic shock, renal failure, bacteriemia, insulin resistance, hypercatabolic state and multiorgan failure syndrome may be observed in relation with severe fluid loss and increased catabolism in patients who have extensive epidermal separation (2, 13). A blood urea nitrogen value of >10 mmol/L and a glucose level of >140 mg/dL have been associated with severe disease (14). Anemia and reduced lymphocyte count have been reported frequently (15). In our study, reduced lymphocyte count (<2 000/mm³) was found in 2 patients, anemia (<12 g/dL) and reduced albumin level (<3,5 g/dL) were found in three patients and increased transaminase levels were found in five patients. During the follow-up period, in-

creased glucose level and dysfunction in renal tubules were observed only in one patient.

In patients with Stevens Johnson syndrome and TEN, bacterial infection, sepsis and septic shock may be observed especially with *Staphylococcus aureus* and *Pseudomonas aeruginosa* (13). A picture of cellulitis caused by *Pseudomonas aeruginosa* developed in one of our patients who had extensive epidermal separation.

There is still no consensus on a definite treatment method for toxic epidermal necrolysis and SJS (2). Early diagnosis, demonstration of the agents, discontinuation of suspicious drugs, early referral to appropriate centers, good nursing services, adequate nutrition, skin care, pain management, debridement for cutaneous findings when necessary, body temperature control, providing fluid-electrolyte balance, prevention of infections, use of antibiotics when necessary, eye care, genital care and gastrointestinal and respiratory supportive therapies are significant elements of the general treatment approach. Systemic steroids and IVIG are used most frequently in medical treatment and treatment options including cyclosporine, plasmapheresis and hemodialysis are required more rarely (16).

The role of corticosteroids in treatment of SJS and TEN is still controversial. Kardaun et al. (17) reported that use of high dose corticosteroid for short-term was helpful. In the retrospective study of Roongpisuthipong et al. (18) published in 2014, it was reported that use of short-term corticosteroid contributed to reduction in mortality rates. However, there are also studies which reported that steroid treatment did not contribute additionally to care therapy (16). In this study, methyl prednisolone was used at an initial dose of 0.5-2 mg/kg/day in all patients and then the dose was tapered (6-30 days).

It has been reported that IVIG treatment administered at an early stage may prevent disease progression in patients with SJS and TEN (16). It is thought that intravenous immunoglobulin treatment inhibits keratinocyte apoptosis by preventing Fas/Fas binding site interaction (1, 2). There is no consensus on the question if IVIG should be given to patients with Stevens Johnson syndrome and TEN as well as on the dose and duration of IVIG treatment. It has been reported that use of intravenous immunoglobulin at a dose of 2 g/kg is safe, but a dose higher than 2g/kg is superior compared to a dose lower than 2 g/kg in terms of positive effect (1, 19).

Although there are many studies suggesting that intravenous immunoglobulin treatment is beneficial, a meta-analysis performed by Huang et al. (20) showed that IVIG had no contribution to lowering the mortality rate in pediatric patients with TEN. Intravenous immunoglobulin treatment was used in seven patients in this study. The diagnosis was TEN in five of these patients and two patients had a diagnosis of SJS/TEN overlap. Although the dose and duration of intravenous immunoglobulin treatment varies by the severity of the disease, it was used at a dose range of 2-3.5 g/kg/dose (2-9 days) in this study.

Another immunosuppressant drug used in treatment of Stevens Johnson syndrome and TEN is cyclosporine. It is thought that cyclosporine shows its positive effects by inhibiting T lymphocyte and macrophage activity and Fas/Fas ligand interaction (9, 19, 21). It has been reported that successful outcomes are obtained with cyclosporine in treatment of patients with a diagnosis of toxic epidermal necrolysis (22). There are studies reporting that cyclosporine is superior to IVIG, corticosteroid and cyclophosphamide in lowering the morbidity and mortality rates (23, 24). In this study, cyclosporine was used in one patient who did not respond to supportive treatment, IVIG and corticosteroid treatment and a positive outcome was obtained.

The rate of sequela is especially high in TEN and the risk of sequela is related with the rate of separation in the skin (1, 2). In the study of Finkelstein et al. (25) conducted with children, the frequency of sequela was found to be 47% and it was reported that sequelae were most frequently in the form of hypopigmentation of the skin and formation of scar tissue. In our study, sequela changes in the form of wound scar and hyperpigmentation were observed after treatment only in two patients. We think that low sequela rates were related with the fact that the patients were in the childhood age group, presented at an early stage and received intensive immunosuppressive treatment.

In conclusion, SJS and TEN occur rarely in the childhood, but they are serious skin diseases with high morbidity and mortality rates. Discontinuation of the suspected drug, wound care, administration of the necessary supportive therapies and early initiation of immunosuppressive therapies significantly contribute to lowering the morbidity and mortality rates. There is still no consensus on treatment of Stevens-Johnson syndrome and TEN and treatment varies from center

to center. For early diagnosis and treatment, patients should be informed about delayed type hypersensitivity reactions which may occur following use of antibiotics, analgesics, antiinflammatory and anticonvulsant drugs which are frequently prescribed in daily practice and should be monitored in terms of these hypersensitivity reactions.

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Informed Consent: Informed consent was obtained from patients who participated in this study.

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