Stevens-Johnson Syndrome in Thai Children: A 29-Year Study

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Background*: Stevens-Johnson syndrome (SJS) is a rare and severe life-threatening hypersensitivity syndrome. The etiology is unclear but is associated with drug exposure or infections and frequently high morbidity and mortality.*
Objective*: To determine etiologies, treatments and complications of Stevens-Johnson syndrome (SJS) in children.*
Material and Method*: A retrospective descriptive study was performed at Queen Sirikit National Institute of Child Health during 1979 and 2007 (29-year study). The authors collected and separated data into three phases from 1979 to 1987, 1988 to 1997 and 1998 to 2007. Diagnosis was confirmed by pediatric dermatologists.*
Results*: There were 189 patients, 56 cases between 1979-1987, 72 cases between 1988-1997 and 61 cases between 1998-2007. The ratio of male to female was 1.6: 1. The range of age was from 2 months to 15 years old with a mean age of 5.5 years. One hundred and sixty-five cases (87%) had a history of drug taking before onset of the rash. The most common drugs exposure were antibiotics in 69 cases (42%), anticonvulsant drugs in 58 cases (35%), non-steroids anti-inflammatory drugs in 8 cases (5%), antimalarial drugs in 4 cases (2%) and unknown drugs in 26 cases (16%). Mycoplasma infections were found in 5 cases (3%). One hundred and nine cases (58%) were treated with systemic corticosteroids. The corticosteroid treatment was increasing from 18% in the first phase to 64% and 87% in the second and third phase respectively. The overall complications were found in 38 cases (20%) included bacterial skin infections in 16 cases (8%), eye complications in 12 cases (6%), hepatitis in 4 cases (2%) and other complications in 6 cases (2%).Ten patients (5%) died from sepsis and underlying diseases. The mortality rate declined from 9% in the first phase to 1.5% in the third phase*
Conclusion*: Etiology of SJS in children was associated with drug exposure with the most commonly implicated drug being antibiotics and anticonvulsants. Corticosteroid may have a role in the treatment of SJS.*

Keywords*: Stevens-Johnson syndrome, Children*

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Stevens-Johnson Syndrome (SJS) is a rare, severe cutaneous adverse drug reaction potentially life-threatening illness characterized by high fever and mucocutaneous involvement.

The incidence of SJS is 1-3 per million persons per year[1,2]. Classification of SJS and TEN has been based on the degree of epidermal detachment[3]. Epidermal detachment of less than 10% of the total body surface area is considered SJS, more than 30% as TEN, and between 10 and 30% as overlap SJS-TEN.

Several studies of SJS have been reported worldwide[4-9]. However, there has been no report of a large series of SJS in children. The authors reviewed the cases of SJS for 29 years at Queen Sirikit National Institute of Child Health which is the tertiary children's hospital in Bangkok, Thailand.

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Material and Method

A retrospective chart review was performed on patients admitted to Queen Sirikit National Institute of Child Health or Children's Hospital. The clinical diagnosis of SJS was made by dermatologists. The patients should have at least two mucous membranes involvement and epidermal attachment less than 10% body surface area involvement. Patients with a diagnosis of erythema multiforme or toxic epidermal necrolyis were excluded from the present study. The authors, collected data into three phases from 1979 to 1987, 1988 to 1997 and from 1998 to 2007 (29 year-study).

The following data were recorded: age, sex, drugs intake, evidence of mycoplasma infection, treatments and complications.

Results

A total of 189 patients were admitted during this period. There were 56 cases between 1979-1987, 72 cases between1988-1997 and 61 cases between 1998-2007. There were 6-7 cases of SJS per year. The ratio between male to female was 1.6: 1. The age ranged from 2 months to 15 years with the mean age was 5.2 $\pm$ 3.6 years (Table 1).

One hundred and sixty-five cases (87%) had a history of drug exposure. The most common drug exposure was antibiotics in 69 cases (42%), anticonvulsant drugs in 58 cases (35%). Among the antibiotics group, penicillin groups (25%) and sulfonamide group (12%) were the most common medications associated with SJS in all phases but the cephalosporin group was the causative drug only in the last ten years (1998-2007). Anticonvulsants were the second cause of SJS (35%) of which phenobarbital (16%), carbamazepine (15%) and phenytoin (4%) were the causative drugs respectively. The other drugs included non-steroid anti-inflammatory drugs 8 cases (5%), antimalarial 4 cases (2%), and unknown drugs 26 cases (16%). The detailed list of drugs is shown in Table 2 and Fig. 1-3.

For mycoplasma infection, the authors investigated in cases that did not have a history of drug exposure. Of this the authors found only 5 cases (3%) that the mycoplasma titer was positive in rising four fold titer.

Treatment of SJS varied based on time of admission and extend of body surface involvement. All patients were treated with cessation of causative drugs and supportive care that included aseptic skin care, adequate nutrition and fluid management. Ophthalmologists' consultations were performed in all cases that had eye involvement.

One hundred and nine cases (58%) were treated with systemic corticosteroids for 1-2 weeks. The corticosteroid treatment increased from 18% in the first phase to 64% and 87% in the second and third phase, respectively. No patients received intravenous immunoglobulin. Complications of SJS in the present study were found in 38 cases (20%). Superimposed bacterial skin infection was the most complication in 16

Table 1. Demographic data of SJS patients in 3 phases

	1979-1987	1988-1997	1998-2007	Total
No of cases	56	72	61	189
Mean age (years)	4.7 $\pm$ 3.3	5.3 $\pm$ 3.6	5.6 $\pm$ 4.0	5.2 $\pm$ 3.6
Range	2 months-13 years	3 months-14 years	6 months-15 years	2 months-15 years
Sex ratio (Male: female)	1.9: 1	2: 1	1: 1	1.6: 1

Table 2. Drug etiologies of SJS

	1979-1987 (n = 56)	1988-1997 (n = 72)	1998-2007 (n = 61)	Total (n = 189)
No of patients with drug exposure	47 (84 %)	67 (93 %)	51 (84 %)	165 (87%)
Antibiotics	18 (38%)	22 (33%)	29 (57%)	69 (42%)
Penicillin	14 (30%)	15 (23%)	12 (24%)	41 (25%)
Sulfonamide	3 (6%)	7 (10%)	10 (19%)	20 (12%)
Cephalosporin	0	0	7 (14%)	7 (4%)
Tetracycline	1 (2%)	0	0	1 (1%)
Anticonvulsants	10 (21%)	32 (48%)	16 (31%)	58 (35%)
Phenobarbital	5 (11%)	17 (25%)	5 (10%)	27 (16%)
Carbamazepine	3 (6%)	11 (17%)	11 (21%)	25 (15%)
Phenytoin	2 (4%)	4 (6%)	0	6 (4%)
Non-steroid anti-inflammatory drugs	3 (6%)	0	5 (10%)	8 (5%)
Antimalarial drugs	3 (6%)	1 (1%)	0	4 (2%)
Unknown drugs	14 (29%)	12 (18%)	0	26 (16%)

cases (8%). Other complications were eye complications in 12 cases (6%), hepatitis in 4 cases (2%) and other complications in 6 cases (2%) (Table 3). Eye complications were keratitis in 4 cases, corneal ulcer in 2 cases, corneal abrasion in 2 cases, trichiasis in 1 case and blindness in 1 case (Table 4). Ten patients (5%) died from sepsis and underlying diseases. The mortality rate declined from 9% from the first phase to 1.5% in the third phase.

Discussion

The present study was the largest study of SJS in children that had a long time case series. In the present study, there were 6-7 cases of SJS per year. Similar to another report in Asian children, the authors found males to be more predominant than females with the mean age of 5.2 $\pm$ 3.6 years[9].

The etiology of SJS in the present study was similar to other studies that drugs were the most common etiology[9-12]. The most common drugs implicated in all phases were antibiotics and anticonvulsants. The penicillin group and sulfonamide group were the most common antibiotics in SJS patients. Among anticonvulsants, besides phenobarbital and phenytoin, the authors found that carbamazepine was

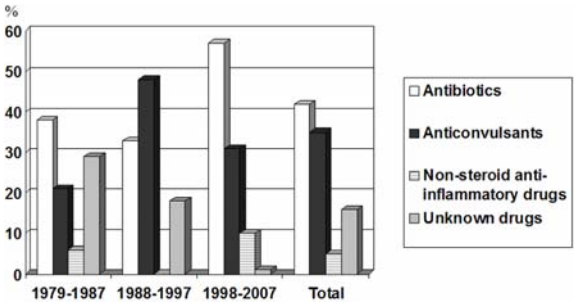

Fig. 1 Drug etiologies of Stevens-Johnson syndrome

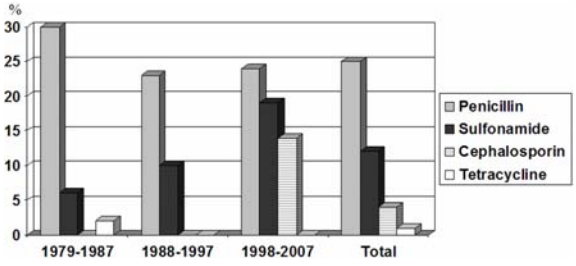

Fig. 2 Drug etiology: antibiotics

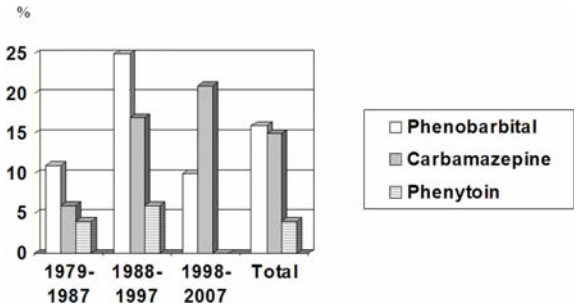

Fig. 3 Drug etiology: anticonvulsants

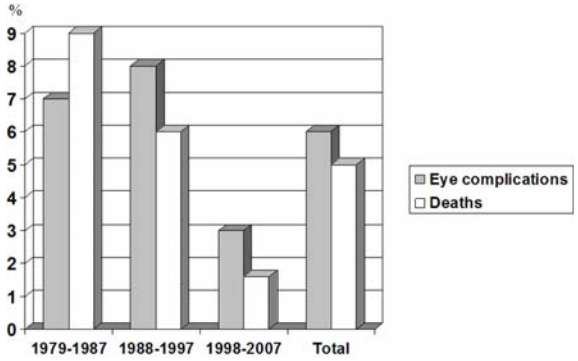

Fig. 4 Serious complications of SJS

Table 3. Treatments and complications of SJS

	1979-1987 (n = 56)	1988-1997 (n = 72)	1998-2007 (n = 61)	Total (n = 189)
No of corticosteroidtreatment	10 (18%)	46 (64%)	53 (87%)	109 (58%)
Total complications	11 (28%)	20 (43%)	7 (1%)	38 (20%)
Eye complications	4 (7%)	6 (8%)	2 (3%)	12 (6%)
Skin infections	3 (5%)	9 (12%)	4 (7%)	16 (8%)
Hepatitis	0	3 (4%)	1 (1%)	4 (2%)
Other complications	4 (7%)	2 (2%)		
		Renal failure 1 case (1%)	0	6 (3%)
		GI hemorrhage 1 case (1%)		
Death	5 (9%)	4 (6%)	1 (1.6%)	10 (5%)

Table 4. Eye complications of SJS

Eye complications	1979-1987 (n = 56)	1988-1997 (n = 72)	1998-2007 (n = 61)	Total (n = 189)
Corneal ulcer	2 (3.4%)	0	0	2 (0.01%)
Trichiasis	1 (1.7%)	1 (1%)	0	2 (0.01%)
Blindness	1 (1.7%)	0	0	1 (0.05%)
Keratitis	0	4 (6%)	0	4 (0.02%)
Ectropion	0	1 (1%)	0	1 (0.005%)
Corneal abrasion	0	0	2 (3%)	2 (0.01%)
Total	4 (7%) 0	6 (8%)	2 (3%)	12 (6%)

the increasing important cause of SJS especially in the third phase. The other uncommon drugs were non-steroid anti-inflammatory drugs. Recently data showed that genetics susceptibility played a role in the pathogenesis of SJS/TEN in Asian patients. Chung found strong association between HLA-B*1502 and carbamazepine induced SJS/TEN among Han Chinese[13]. In Thailand, Lochareonkul found that the prevalence of HLA-B*1502 in Thai patients was 9%[14] and found carbamazepine induced SJS associated with HLA-B*1502 allele in Thai population. In the future, genotyping for HLA-B*1502 may be done before treatment with carbamezepine to decrease the risk of SJS[15].

Beside the drug etiology of SJS, mycoplasma infection was a potentially cause of SJS in children than in adult[16]. In the present study, the authors found mycoplasma infection in only 3% of cases.

Management of SJS includes prompt diagnosis and discontinuation of all suspected drugs. Early withdrawal of the causative drug is associated with a better prognosis[17]. Infectious causes should be sought and treated. Supportive treatment is very important[18-21]. In SJS patients, special attention to fluid requirements, electrolyte balance, intravenous caloric replacement, meticulous skin care and avoidance of secondary infection are important. When ocular involvement is present, ophthalmologic consultation should be obtained.

The role of systemic corticosteroid is controversial but short term administration of intravenous systemic corticosteroid is sometimes advocated if it is started within the first 2-3 days of a drug-induced reaction[22]. Risks of prolonged use of systemic corticosteroid are increasing secondary infections, prolonged wound healing, masking early signs of sepsis and gastrointestinal bleeding. Intravenous immunoglobulin is a useful and safe therapy in severe cases of SJS or TEN which do not respond to systemic corticosteroid[24].

In the present study, the authors increased the use of systemic corticosteroid from 18% in the first phase to 64% and 87% in the second and third phase, respectively. The authors' experience of corticosteroid treatment in SJS shows the advantage of decreasing the duration of the disease and the serious complications such as eye complication as well as the mortality rate.

In conclusion, etiology of SJS in Thai children was associated with drug exposure with the most commonly implicated drugs being antibiotics and anticonvulsants. Corticosteroid may have a role in the treatment of SJS.

Potential conflicts of interest

None.

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สตีเวนส์-จอห์นสันในเด็ก

ศรีศุภลักษณ์ สิงคาลวณิช, วนิดา ลิ้มพงศานุรักษ์

***ภูมิหลัง**: โรคสตีเวนส์-จอห์นสัน เป็นโรคที่พบไม่บ่อยแต่อาการรุนแรง สาเหตุไม่ทราบแน่ชัดแต่เกี่ยวข้องกับการแพ้ยาและการติดเชื้อ ถ้าไม่ได้รับการรักษาอาจเกิดโรคแทรกซ้อนและเสียชีวิตได้*

***วัตถุประสงค์**: เพื่อศึกษาสาเหตุ การรักษาและโรคแทรกซ้อนของสตีเวนส์-จอห์นสันในเด็ก*

***วัสดุและวิธีการ**: ศึกษาข้อมูลย้อนหลังผู้ป่วยโรค สตีเวนส์-จอห์นสัน ที่รับไว้ในสถาบันสุขภาพเด็กแห่งชาติมหาราชินี ตั้งแต่ปี พ.ศ. 2532-2550 (29 ปี) แบ่งการศึกษาเป็น 3 ช่วงคือ ระหว่างปี พ.ศ. 2522-2530 (ช่วงที่ 1) พ.ศ. 2531-2540 (ช่วงที่ 2) และ พ.ศ. 2541-2550 (ช่วงที่ 3) การวินิจฉัยอาศัยอาการทางคลินิกและยืนยันโดยแพทย์ผิวหนัง*

***ผลการศึกษา**: มีผู้ป่วยทั้งหมด 189 ราย อยู่ในช่วงปี พ.ศ. 2522-2530, พ.ศ. 2531-2540 และ พ.ศ. 2541-2550 จำนวน 56, 72 และ 61 รายตามลำดับ อัตราส่วนเพศชาย: เพศหญิง เท่ากับ 1: 1: 6 อายุตั้งแต่ 2 เดือนถึง 15 ปี ผู้ป่วย 165 ราย (87%) มีประวัติได้รับยาก่อนมีผื่น ยาที่พบเป็นสาเหตุได้แก่ยาปฏิชีวนะ 69 ราย (42%), ยากันชัก 58 ราย (35%) ยาแก้ปวดที่ไม่มีสเตียรอยด์ 8 ราย (5%), ยารักษามาลาเรีย 4 ราย (2%) และไม่ทราบชื่อยา 26 ราย (16%) พบสาเหตุจากการติดเชื้อ Mycoplasma 5 ราย (3%) ผู้ป่วย 109 ราย (58%) ได้รับการรักษาด้วยยาคอร์ติโคสเตียรอยด์ ซึ่งมีอัตราการรักษาด้วยยาคอร์ติโคสเตียรอยด์เพิ่มขึ้นจากช่วงที่ 1 ร้อยละ 18 เป็นร้อยละ 64 ในช่วงที่ 2 และร้อยละ 87 ในช่วงที่ 3 ตามลำดับ พบโรคแทรกซ้อน 38 ราย (20%) ได้แก่การติดเชื้อแบคทีเรียที่ผิวหนัง 16 ราย (8%) ความผิดปกติทางตา 12 ราย (6%) ตับอักเสบ 4 ราย (2%) และโรคแทรกซ้อนอื่น ๆ 6 ราย (2%) มีผู้ป่วยเสียชีวิต 10 ราย (5%) สาเหตุเกิดจากการติดเชื้อและโรคที่เป็นอยู่ อัตราการตายลดลงจากร้อยละ 9 ในช่วงแรกเป็นร้อยละ 1.5 ในช่วงที่ 3*

***สรุป**: สาเหตุของสตีเวนส์-จอห์นสันในเด็กสัมพันธ์กับการแพ้ยา ซึ่งยาที่พบบ่อยได้แก่ยาปฏิชีวนะและยากันชัก ยาคอร์ติโคสเตียรอยด์น่าจะมีบทบาทในการรักษาโรคนี้*