A CLINICAL STUDY ON ACUTE OPHTHALMIC MANIFESTATION AND MANAGEMENT OF STEVENS-JOHNSON SYNDROME CONDUCTED AT A TERTIARY CENTRE OF THIRUVANANTHAPURAM, KERALA

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ABSTRACT

BACKGROUND

SJS (Stevens-Johnson Syndrome) is an acute life-threatening immune complex mediated hypersensitivity reaction to drugs that results in extensive necrosis and detachment of the epidermis, which shows widespread lesions affecting mouth, eyes, pharynx, larynx, skin, genitals etc. Acute ocular manifestation caused by SJS causes severe ocular morbidities if not treated at an early stage.

MATERIALS AND METHODS

A descriptive follow-up study was undertaken at Regional Institute of Ophthalmology (RIO), Thiruvananthapuram, Southern Kerala. Patients presented at Dermatology and General Medicine Department of Medical College Hospital, Thiruvananthapuram, identified with SJS were examined and called for detailed ocular evaluation at RIO. A total of 52 cases were screened during August 2009 to 2011 and all patients were told about the severity of disease and their detailed drug history, personal history and ocular symptoms were collected. Protocol based treatments were offered to all subjects and effect of treatment was studied during follow-up periods. Data of the patients was recorded on a prefabricated proforma. Data was statistically analysed to find out association and comparison between different parameters using non-parametric Chi-square (χ^2) test.

RESULTS

23.1% of SJS subjects showed toxicity to ciprofloxacin; 96.2% showed acute ophthalmic manifestation. Catarrhal type of conjunctivitis was the commonest, which responds well to terramycin eye ointment and frequent irrigation of eyes. Corneal erosions and corneal ulceration in the acute period were reduced in the follow-up period due to active ophthalmic intervention in the early period.

CONCLUSION

1. SJS is a life-threatening illness with high incidence of ocular involvement.
2. Conjunctivitis is the commonest acute ophthalmic manifestation.
3. Early interference and active treatment regimen can reduce the events and further extent of corneal involvement.

KEYWORDS

Stevens-Johnson Syndrome, Punctate Epithelial Erosion, Superficial Punctate Epithelial Erosion, Toxic Epidermal Necrolysis.

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BACKGROUND

SJS (Stevens-Johnson Syndrome) is an acute life-threatening immune complex mediated hypersensitivity reaction to drugs that results in extensive necrosis and detachment of the epidermis which shows widespread lesions affecting mouth, eyes, pharynx, larynx, skin, genitals etc. SJS confirmed cases were studied at RIO, Thiruvananthapuram, prospectively and the data obtained were statistically analysed. Ocular manifestation in these studies were conjunctivitis, conjunctival bullae, symblepharon following membranous conjunctivitis and corneal erosions and corneal ulcerations, PEE (Punctate Epithelial Erosions), Superficial Punctate Epithelial Erosions (SPEE) and uncommonly cases of corneal opacity.

Among the acute manifestations, Catarrhal type of conjunctivitis is the commonest followed by mucopurulent type and membranous type. In acute stage symblepharon, the involvement in lower lid was more and they broke on lysis with glass rod and a spatula. Patient with milder skin involvement may still have severe ophthalmologic inflammation and most need prompt and persistent ophthalmologic evaluation during the acute phase. If the patient is critically ill and require specialised nursing and medical care, careful monitoring is a must. Any potentially offending drugs should be discontinued immediately. Management is undertaken as soon as possible in acute cases and be admitted in intensive care units or in burn units. Proper fluid balance management is crucial because of the loss of stratum corneum. Ocular surface hygiene should be monitored with frequent conjunctival irrigation and instillation of prophylactic antibiotics to control secondary infection. Topical steroids were used to relieve scarring to an extent. Milder cases of non-membranous conjunctivitis and non-lid margin involvement or corneal involvement may be managed with daily inspection. In corneal involvement, cycloplegics can also be used to relieve pain, photophobia and ciliary spasm. Topical antibiotics and anti-inflammatory drugs and agents such as cyclosporine or corticosteroid drops may

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be used. To relieve Symblepharon rings or bandage, contact lens can be used to separate between the palpebral conjunctivae from bulbar conjunctivae. Use of lubricating eye drops itself in the acute phase is advocated by some doctors. Early interference and active treatment regimen in the acute phase itself can reduce or prevent in going for late phase ocular complications in this study.

Aim

1. To find out the acute ophthalmic manifestation of patients attending a tertiary eye care hospital in Southern Kerala and their management.
2. To find out the correlation between drug aetiology and ophthalmic manifestations.

Settings

Regional Institute of Ophthalmology (RIO), Government Medical College Hospital, Thiruvananthapuram, Kerala.

MATERIALS AND METHODS

The study was designed as a descriptive follow-up study and patients presented at Dermatology and General Medicines Department of Government Medical College Hospital, Thiruvananthapuram, identified with SJS were examined and called for detailed ocular evaluation at RIO. A total of 52 cases were screened during August 2009 to August 2011 after getting consent from Institutional Human Ethical Committee.

All patients were told about the severity of the disease and their detailed drug history, personal history and ocular symptoms were collected and subjected to detailed ocular examination with slit lamp evaluation of lids, conjunctivae and cornea and anterior chamber. Protocol based treatment were offered to all subjects and effect of treatment was evaluated during the 1st visit and later follow-up periods. Vision acuity was noted initially and follow-up visits.

All patients were informed about the chronicity of the disease. Patient was called for follow-up visit for 2 weeks, 4 weeks, 2 months and 6 months. Data of the patients were recorded on a prefabricated Proforma. Data was statistically analysed to find out association and comparisons between different parameters using non-parametric Chi-square (χ^2) test. For all statistical evaluations, a two-tailed probability of value $p < 0.05$ was considered significant.

RESULTS

Ophthalmic manifestations of 52 SJS patients along southern Kerala, India were investigated, and the results are as given below.

Age Distribution

Age (years) group analysis of the population showed majority of the subjects were between 30 - 39 years (Table 1) and the mean age was 39.56 ± 3.56 . SJS was seen commonly in the 3rd and 6th decade in this study.

Age	Frequency	Percent
< 20 yrs.	7	13.5
20-29	8	15.4
30-39	14	26.9
40-49	8	15.4
50-59	6	11.5
>= 60 yrs.	9	17.3
Total	52	100

Table 1. Age Distribution

Causative Drugs

In the present study, it showed Ciprofloxacin was effective in 12 (23.1%) patients followed by paracetamol 9 (17.3%) and Sulphamethoxazole 8 (15.4%), which was followed by antiepileptics (Phenytoin) and Carbamazepine were effective in 6 (11.5%) and 4 (7.7%) patients respectively. NSAIDS (Brufen) as 3 (5.8%) and other groups of drugs as 5 (9.6%) (Table 2 and Fig. 2).

Drug	Frequency	Percent
No drug intake	2	3.8
Ciprofloxacin	12	23.1
Paracetamol	9	17.3
Ibuprofen	3	5.8
Sulphamethoxazole	8	15.4
Allopurinol	3	5.8
Carbamazepine	4	7.7
Phenytoin	6	11.5
Others	5	9.6
Total	52	100

Table 2. Table showing Causative Drugs

Ophthalmic Manifestations

Ocular involvement was very high in this study. SJS has several ophthalmic manifestations, of which the conjunctival involvements are the major causative reasons for different disease complex or syndromes.

Conjunctival Involvement in Acute Stage

In the acute stage, conjunctivitis was the commonest ophthalmic manifestation and was seen in 50 patients (96.2%) (Table 3 and Fig. 3).

Acute Conjunctival Involvement	Frequency	Percent
Catarrhal	26	50.0
MPC	10	19.2
Membranous conjunctivitis	9	17.3
Others	5	9.6
Total	52	100

Table 3. Conjunctival Involvement in Acute Stage

Types of Conjunctivitis in the Acute Stage

In this study, commonest type of conjunctivitis is catarrhal conjunctivitis (50%) (Table 4a).

Types of Conjunctivitis	Percent
MP	19.20%
MC	17.30%
Others	9.60%
Absent	3.80%
Catarrhal	50.00%

Laterality of Conjunctivitis in the Acute Stage

Laterality of conjunctivitis is bilateral, i.e. frequencies in Right and Left eye is 100% (Table 4b).

Conjunctival Involvement	Right Eye		Left Eye	
	Frequency	Percent	Frequency	Percent
Absent	2	3.8	0	0.0
Catarrhal	26	50.0	28	53.8
MP	10	19.2	10	19.2
MC	9	17.3	9	17.3
Others	5	9.6	5	9.6
Total	52	100	52	100

Chi-square: 0.658; P > 0.05

Table 4. Table showing Laterality of Conjunctivitis in the Acute Stage

Symblepharon in Acute Stage

The present study showed symblepharon in 10 eyes and they broke on lysis with glass rod and a spatula and relieved by cutting the band. About the symblepharon involvement upper eye lid involvement in right eye as 3.8% and left eye as 5.8% and in lower eye lid involvement in right eye as 13.5% and left eye as 13.5% as similar to other hospital-based studies (14%).

Acute Symblepharon	RE	LE
Absent	82.70%	80.80%
Upper lid	3.80%	5.80%
Lower lid	13.5%	13.5%

Chi-square: 0.879; P > 0.05

Table 5. Acute Symblepharon

Membranous Conjunctivitis

9 patients showed membranous conjunctivitis (17.3%), 5 patients showed other type of conjunctivitis (9.6%).

Corneal involvement in Acute Stage

The present study showed corneal involvement in acute stage, also Corneal involvement erosions were shown by 9 (17.3%) and Superficial Punctate Epithelial Erosions (SPE) were shown by 7 (13.6%) of the total study population. Punctate Epithelial Erosions (PEE) were shown by 12 (23.3%) and SPEE were shown by 7 (13.6%).

Corneal opacity were noted in 3 (5.7%) patients, uncommonly corneal opacity occur during acute phase. Among these, three cases of initial or very early ophthalmic interference could not succeed. The incidence of acute corneal corrosion presented in 9 patients were reduced to 3 in the follow-up period and 12 of patients presented with PEE were reduced to 5 in the follow-up period followed by SPEE. This shows active and early ophthalmologic intervention and meticulous treatment regime can reduce the corneal involvement to certain extent. Chi-square test conducted in this group (p < 0.001) showed significant reduction in the incidence of corneal involvement in the follow-up period.

Figure 1. Acute Conjunctival Involvement

Acute Corneal Involvement	Frequency	Percent
PEE	12	23.1%
Erosion	9	17.3%
SPEE	7	13.6%
Corneal opacity	3	5.7%
Absent	21	40.4%
Total	52	100%

Table 6. Table showing Corneal involvement in Acute Stage

Figure 3

DISCUSSION

SJS causes mucosal erosions with widespread erythematous cutaneous macular or target lesions that merge together with subsequent epidermal detachment. Previous studies shown about drug responsibility is 55.99% of SJS. All age groups are affected, but incidence however appear to have peaked in the second (Thomas, 1950; Duggan and Gaines, 1951) and fifth decade. Approximately 6 cases/ million persons/ year were affected.^{1,2} (Schopf et al, 1991; Roujeau et al, 1995) reported an overall risk of 0.93/ millions persons/ year for Toxic epidermal necrolysis and 1.1 per million persons/ year for SJS. Again, Roujeau et al (1995)¹ describes an incidence of 1.2 to 1.3 cases per million/ year for toxic epidermal necrolysis and 1.1 per million persons/ year for SJS.

Recent studies revealed genetic susceptibility to a certain extent as in some East-Asian population studies HLA Class I marker in Japanese patients with carbamazepine-induced cutaneous adverse reactions (Ikeda et al, 2010).³ A significant majority of patients with Acute SJS/ TEN will have ophthalmic pathology. According to Storm (1996),⁴ he found that eyes are very often affected 93% and called it as a mucocutaneous ocular fever. Studies by Power et al (2007)⁵ and Chang et al (2011)⁶ reported ocular involvement in 69% and 81% respectively of patients with SJS and TEN. Yip (2005)⁷ reported acute ocular involvement in 69% of SJS/ TEN patients. The type and severity of ocular involvement seems to have no relation to the extent of severity of systemic disease (Duggan and Gaines, 1951).⁸ The incidence of ocular involvement during the acute phase has been reported to be between 69% and 82% for SJS and 50% and 88% for TEN (Pushker et al, 2000; Power et al, 2007).^{5,9}

Conjunctivitis is the most frequent involved structure in the eye in SJS (Thomas, 1950; Duggan and Gaines, 1951).^{8,10} Pohloja and Fleimo (1966)¹¹ and Stewart et al (1994)¹² reported conjunctivitis in 82% of cases of SJS. It is usually bilateral (Ashby and Lazar, 1951; Ting and Adam, 1985).^{13,14} The bilateral conjunctivitis may be catarrhal or pseudomembranous and occur in 15% to 75% patients with SJS (Bianchine et al, 1968).¹⁵

A more severe conjunctival lesions results in pseudomembranous or membranous conjunctivitis as reported by Foster et al (1988),¹⁶ which may often lead to catarrhal conjunctivitis. Commonest type of conjunctivitis is the catarrhal type. But few authors (Duggan and Gaines, 1951; Howard, 1963; Strom, 1966)^{8,17,4} states purulent conjunctivitis and pseudomembranous were the commonest manifestations. Misra and Chandi Das (1968)¹⁸ described a case of SJS with severe bilateral congestion of bulbar and tarsal congestion of conjunctivae with profuse mucopurulent discharge.

Conjunctival Chemosis

Reported by Power et al (2007)⁵ in acute phase.

Lid-Globe Adhesions

Power et al (2007)⁵ reported lid-globe adhesions in many cases of SJS.

Conjunctival Bullae

As an acute manifestation noticed by Ashby and Lazar (1951)¹³ and Champion et al (1998).¹⁹

Corneal Involvement

Corneal erosions and ulcerations occur in the acute stage of SJS and TEN reported by Howard (1963),¹⁷ Wilkins et al (1992)²⁰ and Albert et al (1994).²¹ It can lead to perforation also (Shah et al, 1977).²² 12 of 20 (60%) cases of SJS reported by Sarkari et al (1972)²³ had corneal involvement. Champion et al (1998)¹⁹ also described about corneal ulceration. Shaffer and Morris (1948)²⁴ reported a case of corneal perforation occurred in one eye in acute phase and in two cases almost complete blindness resulted from corneal ulceration. Anterior uveitis occur in acute stage of SJS reported by Huff et al (1983)²⁵ and Wilkins et al (1992).²⁰

In the acute phase itself, active interference by some local measures plays an important role to prevent ocular morbidity to some extent.

Important role measure advocates include:- Tear film substitute, frequent irrigation of fornix, removal of pseudomembrane, lysis of symblepharon using glass rod and topical antibiotics to prevent secondary infection, topical steroids to prevent scar formation, topical cycloplegics to prevent pain, photophobia and ciliary spasm and corneal epithelial integrity by pad and bandage.

Causative Drugs

In the present study showed ciprofloxacin effective in 12 (23.1%) patients followed by paracetamol 9 (17.3%) and Sulphamethoxazole 8 (15.4%), which was followed by anti-epilepticus (Phenytoin) and Carbamazepine were effective in 6 (11.5%) and 4 (7.7%) patients respectively. NSAIDS (Brufen) as 3 (5.8%) and other groups of drugs as 5 (9.6%) (Table 2 and Fig. 2). Data from surveillance network cited by Roujeau et al (1995)¹ on 245 people hospitalised for SJS reported risk factors was oral intake of 80% NSAIDS and similar observations were also reported by Storm (1966).⁴ But in this study, Brufen contributes only (5.8%) as an aetiological factor and also mentioned about new users of antiepileptic adverse reactions as an aetiological factor. In the present study, antiepileptic contributes 19.2%. A survey of selected patients with epilepsy over 80% has reported at least

one adverse event and the majority had more than one adverse event (Pushker et al, 2000).⁹

Ophthalmic Manifestations

Ocular involvement was very high in this study. A retrospective study conducted at National Cheng King University Hospital in Taiwan between 1988 – 2004 attackers of SFS/ EM of 207 patients showed SJS in high ophthalmic involvement (81.3%) (Yip, 2007).⁷

Conjunctival Involvement in Acute Stage

Stewart et al (1994)¹² has also conjunctival involvement in 82% cases with SJS. In the acute stage, catarrhal type of conjunctivitis was the commonest and was manifested in 50% study population. This is in concordance with the findings of a study conducted by different investigators like Duggan and Gaines (1951),⁸ Howard (1963)¹⁷ and Storm (1966)⁴ in which at least 10% showed mucopurulent conjunctivitis.

Misra and Chandi Das (1968)¹⁸ described cases of SJS with bivalent severe bulbar, tarsal congestion of conjunctivitis with profuse mucopurulent conjunctivitis which responds with terramycin eye ointment and frequent irrigation of eyes.

Membranous conjunctivitis was shown by 9 (17.3%). Other acute manifestation like conjunctival chemosis was shown by 9.6%. It was noted more in the patients who had taken sulpha drugs.

Types of Conjunctivitis in the Acute Stage

In this study, commonest type of conjunctivitis is catarrhal conjunctivitis (50%) (Table 5). This was in correspondence with the findings of a study conducted by Duggan and Gaines (1951),⁸ Howard (1963)¹⁷ and Storm (1966).⁴

Symblepharon in Acute Stage

A study at Tan Tock Seng Hospital, Singapore reported 85 patients out of 117 patients who were being SJS and symblepharon were shown by 6 (14%) in acute period. 10 showed mucopurulent conjunctivitis (19.2%). In a study by Misra and Chandi Das (1968)¹⁸ described a case of SJS with bivalent severe bulbar and tarsal congestion of conjunctivitis with profuse mucopurulent conjunctivitis, which responded well to terramycin eye ointment and frequent irrigation of eyes.

Membranous Conjunctivitis

9 patients showed membranous conjunctivitis (17.3%), pseudomembranous conjunctivitis has been reported by Wolff (1949).²⁶ In this study 5 patients (9.6%) showed other types of conjunctivitis.

Corneal involvement in Acute Stage

Corneal involvement erosions were shown by 9 (17.3%) and Superficial Punctate Epithelial Erosions (SPE) were shown by 7 (13.6%) of the total study population. Howard (1963) and Wilkins et al (1992)²⁰ reported that corneal erosions and ulceration occur in the acute stage of SJS.

Punctate Epithelial Erosions (PEE) were shown by 12 (23.3%) and SPEE were shown by 7 (13.6%). A study conducted at LV Prasad Eye Institute, Hyderabad, revealed SPEE as noticed in 51 patients out of 95 (Misra and Chandi Das, 1968).¹⁸

Corneal opacity were noted in 3 (5.7%) patients, uncommonly corneal opacity occur during acute phase. Among these, three cases with initial or very early ophthalmic interference could not succeed. But Ward et al (2010)²⁷ in their series mentioned destruction of the corneal limbal stem cells was perhaps the most due. Consequences of the aforementioned pathologies can lead to vascularisation and thickening of the corneal epithelium.

The incidence of acute corneal corrosion presented in 9 patients were reduced to 3 in the follow-up period and 12 of patients presented with PEE were reduced to 5 in the follow-up period followed by SPEE. This shows active and early ophthalmologic intervention and meticulous treatment regimen can reduce the corneal involvement to certain extent. Chi-square test conducted in this group ($p < 0.001$) showed significant reduction in the incidence of corneal involvement in the follow-up period.

A hospital-based other studies (Hallgren et al, 2003)²⁸ revealed more adverse reactions to Antiepileptics. In our study showed drug toxicity to NSAIDS (Brufen) as 3 (5.8%) and other groups of drugs as 5 (9.6%). A study conducted by Roujeau et al (1995)¹ on 245 hospitalised SJS patients also showed risk factor as oral intake of NASIDS 80%.

About the acute ophthalmic manifestation, ocular involvement was very high in this study as similar to a hospital-based study conducted at Taiwan between 1988 – 2004 (Yip, 2007)⁷ on attackers of SJS/ Epidermal necrolysis of 207 patients showed high ophthalmic involvement (81.3%).

Acute ophthalmic manifestation like acute stage conjunctivitis was the commonest manifestation and was seen in 50 patients (96.2%), higher than other study (82%) (Yip, 2007).⁷

The acute stage catarrhal type of conjunctivitis was the commonest and was seen in 50% of the total population of the present study. This was in concordance with the earlier study conducted by Duggan and Gaines (1951).⁸ In our study, Mucopurulent Conjunctivitis (MPC) reported in 19.2%, similar to other studies conducted by Misra and Chandi Das (1968),¹⁸ which revealed cases of SJS with profuse mucopurulent conjunctivitis which responds with terramycin eye ointment and frequent irrigation of eyes.

Discussing about the laterality of conjunctival involvement, it seems bilateral i.e. frequencies in right and left eyes is 100% as similar to a study conducted by Ting and Adam (1985).¹⁴

A hospital-based study conducted by Wilkins et al (1992)²⁰ says corneal erosions and ulceration occurs in acute stage of SJS. In this study, punctate epithelial erosions were shown by 12 (23.1%).

Corneal opacity was noted by 3 (5.7%). But in these three cases, initial or very early ophthalmic interference could not succeed. But a study conducted by De Rojas et al (2007)²⁹ reported destruction of the corneal limbal stem cells, perhaps the most due consequences of the aforementioned pathologies and can lead to vascularisation and corneal epithelial thickening.

Thus, the present study emphasises on the importance of meticulous screening on ocular manifestation in the acute phase and if offered proper treatment modalities can minimise the visual impairment due to ophthalmic morbidities caused by Stevens-Johnson Syndrome.

CONCLUSION

SJS is a life-threatening illness with high incidence of ocular involvement. Conjunctivitis is the commonest acute ophthalmic manifestation. Early interference and active treatment regimen can reduce the events and further corneal involvement.

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