Stevens-Johnson Syndrome, Pathophysiological Aspects: A literature review

OLIVEIRA, Alex Ferreira de [1]

SILVA, Ingrith do Socorro Neves da [2]

BRITO, Lídia Pinheiro de [3]

PEREIRA, Rebeca Luiza Abreu [4]

FECURY, Amanda Alves [5]

DIAS, Cláudio Alberto Gellis de Mattos [6]

DENDASCK, Carla Viana [7]

OLIVEIRA, Euzébio de [8]


SUMMARY
The aim of this work was to verify in the literature the basics, pathophysiology, diagnosis, causes, signs, symptoms and treatment of Stevens Johnson Syndrome (SSJ). Left-a literature review, which provided results analyzed systematically. 22 scientific publications were selected registered in virtual Health Library (VHL), Scielo and LILACS, edited in the period from 2003 to 2012. It was found that the publication of articles was growing, but few texts are available. Identified that the suspect SSJ make the drug suspension inductor, and monitored treatment in burn unit or intensive care, for control of the electrolytic balance, nutritional support and prevention of infections. The inadequate service to the individual is a risk factor for occurrence of death. Were also detected the following risk factors for the development of this type of reaction: HIV, Lupus Erythematosus, bone marrow transplantation, use and drug doses higher than those recommended or rapid increase in dose.

Keywords: Stevens Johnson Syndrome; Publications; Risk factors.

1 INTRODUCTION

Stevens-Johnson Syndrome (SSJ) can be defined as a framework of an acute inflammatory disease pathophysiological, feverish and self-limiting, lasting approximately two to four weeks, which affects the skin and the mucous membrane. The syndrome usually begins after the use of medications or occurrence of infections and probably introduces autoimmune pathogenesis. She shows no known etiology, however, probably comes from an immune disorder, with the involvement of superficial vessels, resulting in this pathological process (FUCHS, 2008).

It is characterized by skin and mucous membrane reactions potentially fatal result from hypersensitivity to precipitating factors, such as infections by viruses, fungi, bacteria, diseases of the connective tissue, malignant neoplasms, multiple vaccines and medicines. The oral mucosa, conjunctiva and lips are the main regions involved (Falcon, 2008).

The eye frame is characterized by a purulent catarrhal conjunctivitis, diphtheritic membranous or bilateral. In the chronic phase, most patients presents numerous amendments of the ocular surface that may compromise visual acuity, highlighting symblepharon, entropion, ectropion, trichiasis, dry eye, corneal conjuntivalização and keratinization (NOGUEIRA, 2003).

The incidence of SSJ is estimated between 1 to 6 cases per one million inhabitants. Although rare, this condition generates a strong emotional, social and economic impact, because it is a chronic entity that potentially leads to blindness in young patients (NOGUEIRA, 2003).

The treatment of Stevens-Johnson Syndrome is usually symptomatic and support: meticulous care must be made with the skin and mucous membrane, similar to a burn patient, in addition to daily and follow-up
ophthalmologic evaluation for long term. In addition, you must perform the suspension or replacement of the use of drugs that have been linked to the appearance of skin lesions (FUCHS, 2008).

Although the Stevens-Johnson Syndrome is a pathological phenomenon of rare occurrence, presents serious implications that can endanger the patient's life. It is important that the professional be aware of the initial manifestations of this type of Pathology, in order to achieve early diagnosis and, along with the medical staff, can request the return or interruption of use of medication promoter of Pathology, thus decreasing the likelihood of progression to a more serious, or even death (BRAZIL, 2011).

Stevens-Johnson Syndrome is often associated with the use of carbamazepine (CBZ) a well-tolerated anticonvulsant, used to ease the pain of the herpes zoster (HZ), which has as its main complication to post-herpetic neuralgia, thus resulting in severe skin reactions. These are considered immuno-mediated reactions to medication and can be characterized as hypersensitivity syndrome due to seniority of farmacogenéticas and immunological abnormalities to the drug. It presents clinically with erythema, necrosis and extensive epidermal detachment, mucosal involvement and systemic symptoms. The rapid diagnosis knowledge becomes essential, because the withdrawal of the drug is often the most important action to minimize the resulting morbidity (GARCIA, 2010).

Several studies show that medicines are important resources for health recovery, once that improve health and treat disease, and could promote confidence and participation in the services. However, the use of medicines presents risks. Even with the strict criteria of protection and safety, which are required by the Ministry of health, several factors expose users to unwanted effects caused by medicines (BRAZIL, 2011).

The adverse drug reaction (RAM) is among the 10 leading causes of mortality. Despite the advancement of pharmacovigilance in the world, the adverse effects, known or not, of medicines marketed still carry great impact to the health of individuals. For this reason, it is of great significance to rational use of medicines (ANVISA, 2011).

The proper use of medicines, also called for rational use of medicines (RUM), includes appropriate indication to the situation, distribution/dispensing clinic according to the individual needs and administration/correct use (WHO, 2005).

Access to medicines, in turn, indicates the relationship between the need for medicines and supply them with quality (LUIZA; BERMUDEZ, 2004). Access is the first component of the URM. In the hospital environment, the activities carried out by various pervades URM departments/sectors/services involving different professional categories (TORRES; CASTRO, 2007).
The term adverse event (and) the appearance of a health problem caused by the care and not the underlying disease, resulting in temporary or permanent incapacity, and can even evolve into death. Many adverse events originate from surgical procedures, use of medications, medical procedures, delay or inaccuracy in the diagnosis (MENDES et al., 2005).

You can tell, from the concept of adverse event to medicine (EAM), which for the pharmacological treatment have the desired effect should consider both the effectiveness and the safety of the medicinal product as all procedures involved in the process. Then arises the need to differentiate the component responsible for the EAM (BRAZIL, 2004).

The MSA are sub-divided into two groups. The first, called adverse reactions to medicines, relates to the risk inherent in front of the appropriate use of medicines, therefore, inevitable. The other, set to medication errors, understood as any preventable event, arising from the improper use or non-use of needed medicines, therefore, possibly related to failure (FUCHS, 2008).

The reality leaves no doubt as to the importance of identifying and knowing the adverse reactions to medicines, with the objectives to prevent and reduce morbidity and mortality related to them. This purpose will be achieved with the participation of health professionals, of the regulation, control and supervision and enterprises involved in the production and marketing of medicines in the monitoring of reactions (DELUCIA, 2007)

The general objective of this work was to analyze the basic concepts, diagnosis, causes, signs, symptoms and treatment of Stevens Johnson Syndrome.

2 MATERIALS and methods

Descriptive study developed through review of the scientific literature, based on publications available on the banks of electronic databases: virtual Health Library (VHL), Scielo and LILACS.

Second (PEREIRA, 1995) the descriptive studies aim to inform about the distribution of an event, in the population, using the incidence and the prevalence, identifying risk groups, informing about their needs and their characteristics, benefiting in some way taken measures for a given problem, taking into account the epidemiology as the basis of disease prevention and health planning.

For the purposes of this study, search in the data base described above, using the following terms: "Stevens Johnson Syndrome"; "RAM"; "Adverse Reaction"; "Medicine". The terms were employed in isolation and in combination in an attempt to reach the greatest number of articles possible.
The inclusion criteria used were: full texts, written in Portuguese and/or Spanish, published in the period from 2003 to 2012, presenting basic concepts: pathophysiology, diagnosis, causes, signs, symptoms and treatments for the syndrome.

The results were organized into groups of patho-physiological characteristics of information SSJ and characteristics of publications, for composition of paintings and graphics.

3 RESULTS

Met a total of 1,813 articles available about Stevens Johnson Syndrome (SSJ). Applying the inclusion criteria, identified that 726 corresponded to articles between 2003 and 2012, and 100 were full text, as shown in the table 1, below.

Table 1. Articles about SSJ available in the databases searched

<table>
<thead>
<tr>
<th>Database database</th>
<th>Number of publications</th>
<th>Year</th>
<th>Full text</th>
</tr>
</thead>
<tbody>
<tr>
<td>SciELO</td>
<td>1</td>
<td>2006</td>
<td>1</td>
</tr>
<tr>
<td>VHL</td>
<td>62</td>
<td>2003</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>2004</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>2005</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>54</td>
<td>2006</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>101</td>
<td>2007</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>79</td>
<td>2008</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>88</td>
<td>2009</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>117</td>
<td>2010</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>117</td>
<td>2011</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>2012</td>
<td>0</td>
</tr>
<tr>
<td>LILACS *</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Same items found in the Virtual Health Library (VHL).
32 articles, considered the 100 complete texts, as were those presented in Portuguese (n = 16) and Spanish (n = 16). So was the assessment of interest categories, resulting in 22 articles that have fulfilled all criteria for inclusion.

The information of the selected articles were divided into 22: features pertaining to articles and features relating to Stevens Johnson Syndrome, for better presentation of the results.

The characteristics relating to articles, surveyed in this study were: author/year; type of study; Publishing magazine and the profession of the researchers responsible for the publications on the topic. All are arranged in table 2.

Table 2. Features articles about SSJ selected for the study

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Type of study</th>
<th>Publishing magazine</th>
<th>Profession of the researchers</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANVISA 2011</td>
<td>Bibliographical Review.</td>
<td>Rev. pharmaceuticals and Medicines.</td>
<td>Pharmacist; Doctor</td>
</tr>
<tr>
<td>BISHARA 2011 Brazil. 2004</td>
<td>Bibliographical Review.</td>
<td>Rev. of forensic medicine.</td>
<td>Doctor</td>
</tr>
<tr>
<td>Brazil. 2011</td>
<td>Bibliographical Review.</td>
<td>World Health magazine.</td>
<td>Nurse; Doctor</td>
</tr>
<tr>
<td>Brazil. 2011</td>
<td>Bibliographical Review.</td>
<td>Health Magazine For Everyone.</td>
<td>Not Reported</td>
</tr>
<tr>
<td>FONTELES, et al. 2009</td>
<td>Bibliographical Review.</td>
<td>Medical Clinic Magazine.</td>
<td>Pharmacist; Dentist; Doctors; Nurse; Doctor</td>
</tr>
<tr>
<td>GARCIA, J.B.S. 2010</td>
<td>Case report.</td>
<td>Journal of Anesthesiology.</td>
<td>Not Reported</td>
</tr>
<tr>
<td>HARADA, et al. 2011</td>
<td>Case report</td>
<td>Rev. Doctor Ana Costa</td>
<td>Doctor; Nurse Pharmacist; Doctors; Doctor</td>
</tr>
</tbody>
</table>
Identifies a large frequency of doctors participating in the publications (n = 18, 53%), followed by pharmacists (n = 7, 20%), nurses (n = 6, 18%), psychologists (n = 2, 6%) and dentist (n = 1, 3%). In some publications were only available to titration of the researchers, in these cases all were teachers or doctors in public health.

Among medical researchers, have been specialties: Anesthesiology, dermatology, surgical clinic, general practitioner, embryology, obstetrics and ophthalmology.

About the patho-physiological characteristics associated with Stevens Johnson Syndrome, presented in articles surveyed, stood out: population with a higher risk of developing the disease; most associated with the syndrome; complications of the syndrome; emergency treatment and curative treatment, structured in table 1.

**Table 1. Patho-physiological characteristics of SSJ broadcast articles searched**

<table>
<thead>
<tr>
<th>Population with greater risk</th>
<th>Children and the elderly because they are more immunologically vulnerable and 30 years of age group.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medications associated with SSJ</td>
<td>Carbamazepine, Ciprofloxacin, Penicillin, Sulfa Drugs.</td>
</tr>
<tr>
<td>Complications of SSJ</td>
<td>Increase of leukocytes, alteration of liver markers, low immunity, oncological diseases, nephritis, myocardial injury, eye sequels, acquired immunodeficiency syndrome, death.</td>
</tr>
<tr>
<td>Emergency Treatment</td>
<td>Immediate suspension of the drug suspect: The patient must be admitted preferably in hospitals able</td>
</tr>
</tbody>
</table>
Curative Treatment

Care should be made initially with support and symptomatic measures: hydration and electrolyte replacement, special care the Airways, ambient temperature control, careful handling and aseptic sterile field creation, maintenance of peripheral venous access away from affected areas.

Source: data compiled by the authors.

The presence of categories of interest (basic concepts, diagnosis, causes, signs, symptoms and treatments for Stevens Johnson Syndrome), established as inclusion criteria for the assessment of articles, were also evaluated and quantified for description of results (graph 1).

| Chart 1. Distribution of articles that showed interest for research of SSJ |
| 12 (25%) Conceitos Básicos |
| 11 (23%) Diagnóstico |
| 13 (27%) Causas |
| 8 (17%) Sinais e Sintomas |
| 4 (8%) Tratamentos |

Identified that the broadcast are the signs and symptoms; basic concepts and treatments, respectively.

4 DISCUSSION

The SSJ is a type of skin reaction that causes a rash, followed by bleeding cracks. Nishiyama et al. draws attention to the link that surrounds the patients treated with anticolvusionantes, antidepressants,
benzodiazepines, antiparkinsonianos, neurolépticoe antimicrobanos, because these classes of medicine can result in adverse effects on the patient, regardless of the treatment be in outpatient or hospital scheme.

Usually, the diagnosis of SSJ is clinical, based on the findings in the patient's body (blisters and ulcerations) and the health history of this. Although the dermal tissue isn't the only one that can be compromised, because the syndrome is an acute manifestation, which can result in internal complications: liver lung and other general order, as for example, nephritis and myocardial injury.

There is displacement of the epidermis, the skin leaving it looking burn. In fact, the understanding that one has from the analysis of the results is explained in material that SSJ is compatible to the third-degree burn, hence the need for intense hydration of the patient, as a way to minimize the pain and recover the body, which is devoid of liquid, absorbed by high temperature. The suspension of the drug causing or suspected of having caused the syndrome must be the first action of the doctor about the affected patient.

A way to prevent allergic reactions by consciously drugs is not to use them on their own, because only the doctor is able to assess each case and prescribe the medication, not even the patient free of adverse reactions, which according to the different organisms may cause unforeseen reactions, and higher when it comes to drug interaction in patients polimedidos. This is a smart way to avoid problems related to the use of medicine.

Generally patients with SSJ received support measures similar to those administered in patients with burn and dehydration to overcome the crucial moments and uncomfortable due to various symptoms reserved to concerned.

The SSJ is a rare, but when it affects a person can leave permanent physical and psychological marks. On average, once treated, the acute phase of the syndrome can be reversed between two and four weeks, although between the results recorded in articles, cases of patients affected by SSJ which evolved to death, after the twelfth day of hospitalization and monitoring in intensive care center (CTI). Generally the deaths occurred by septicemia, leading to clinical complications that led to death.

The studies work with an age range of 30 years to indicate people more apt to develop the syndrome, suggested because it is an age when the high production level of individuals, leads to greater exposure, with more chance of using drugs, physiological changes and immunological changes associated with adverse drug reaction.

In the case of the studies identified an increase of articles published over the years, where he raises some hypotheses for the occurrence: greater interest in publishing the theme in databases, taking out the information before comprised institutional reports; higher frequency of acometimentos of the syndrome
because of medicalization, with greater exposure of individuals to medication; greater understanding of the complex process that involves the manifestation of the syndrome.

In this context, the greatest number of complete texts available also allows better access to the information related to the SSJ. This factor decreases the amount of professionals who are unaware of the disease and facilitates recognition of the problem in question.

It was observed that most of the work was of type literature review, because it is a rare involvement, low frequency in the population, hindering the development of research as clinical trials. More cohort studies or case control must be developed to help in deepening the theme. In addition, most professionals must search on the topic, since much of the research and publications have been made by doctors.

The medical professional seems to be most interested in the subject, perhaps because of the need to establish the diagnosis with brevity and establish the profile of treatment properly to avoid sequelae and/or death of the patient.

CONCLUSION

Several articles found debated what would suit the Stevens Johnson Syndrome, its causes, how to get to your diagnosis, signs and symptoms, followed by numerous forms of treatment and care to the bearer of the syndrome.

This study brings to light that the clinical detected on physical examination on admission were injuries to face, conjunctiva, mucous membranes – mucositis bleeding-lips, chest, abdomen and tachycardia, joint presentations on Stevens Johnson Syndrome. Such manifestations occur after treatment with antibiotics, anticonvulsionante and Neuroleptics, and in all cases the drugs suspects were suspended, with immediate symptomatic treatment initiated: analgesias and constant hydration.

Additional care should be taken with elderly polimedicados patients and patients treated with the medications capable of presenting allergic process that progresses to the SSJ.

Other risk factors detected for the development of this type of reaction are related to HIV, Lupus Erythematosus and bone marrow transplantation.

REFERENCES


FORBES et al., *medicated Cutaneous adverse reactions Stevens Johnson Syndrome and toxic epidermal necrosis*, revised guide to adverse reaction to medicines, Rio de Janeiro 2011, p. 32-39


2011.


Luiza, Bermudez. Access to medicines: concepts and controversies. In:

Bewrmudez LIES, Oliveira MA, Escher (org.). **Access to medicines: derecho**


THE WORLD HEALTH ORGANIZATION. **Drug safety: a guide to detect and report adverse reactions to drugs**. p. 1-20, 2005


PEYRIÉRE, et al., **Dress Syndrome and Steven Johnson.** Search Legal Medicine, vol. 28 (1), mar 2011, 1409-0015.


[1] Pharmacist. Master in pharmaceutical sciences. Professor and researcher at Metropolitan College FAMAZ from Amazon. Pharmacist University Hospital Barros Barreto (HUJBB) – PA-email: autor@nucleodoconhecimento.com.br

[2] Travel nursing academic FAMAZ-Faculdade Metropolitana da Amazônia-email: autor@nucleodoconhecimento.com.br
[3] Travel nursing academic FAMAZ-Faculdade Metropolitana da Amazônia-email: autor@nucleodoconhecimento.com.br

[4] Travel nursing academic FAMAZ-Faculdade Metropolitana da Amazônia-email: autor@nucleodoconhecimento.com.br

[5] Biomedical. Doctorate in Tropical Diseases. Lecturer and researcher at the Federal University of Amapá, AP. Collaborator researcher of the Center for Tropical Medicine UFPA (NMT-UFPA)-email: autor@nucleodoconhecimento.com.br


[7] Theologian, doctor of Clinical Psychoanalysis, a researcher at the Center for research and advanced studies-CEPA-email: autor@nucleodoconhecimento.com.br