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CLINICAL ASPECTS OF STEVENS JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS: LITERATURE REVIEW

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Abstract: INTRODUCTION: Pharmacodermias are emergency drug reactions that can occur due to the use of any medication, since the WHO (World Health Organization) defines such reactions as unintentional damage caused by the use of drugs in usual therapeutic, prophylactic or diagnostic doses. Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are spectra of the same clinical entity. **OBJECTIVES:** The aim of this study is to list the clinical characteristics of SJS and TEN, differentiating both pharmacodermias, and to analyze their possible therapeutic approaches. **METHODOLOGY:** The methodology chosen was a literature review, in the form of a systematic review, based on the study of references already analyzed and ratified by written and electronic means. **RESULTS AND DISCUSSION:** Drug reactions can have immunological or non-immunological mechanisms, with the type IV hypersensitivity reaction being the reaction related to SSJ and NET. The distinction between the two conditions is clinical, with epidermal detachment in SJS being less than 10%, and the main causative medications being anticonvulsants, NSAIDs and sulfa drugs, generating multiple cutaneous-mucosal involvement. NET, on the other hand, has a detachment of more than 30% and is a severe bullous condition with the appearance of large burns. The treatment of these conditions should be carried out in Intensive Care Units, and the SCORTEN, a prognostic score, can be applied. **CONCLUSION:** However, when prescribing medication, medical professionals should always bear in mind the possible adverse drug reactions that may occur.

Keywords: Dermatology; Drug Hypersensitivity Syndrome; Stevens-Johnson Syndrome; Common Tegument.

INTRODUCTION

When using any medication, everyone should be aware of the possibility of some unwanted effect, sometimes adverse reactions can be emergency, as in pharmacodermias. (Evandro; Rivitti, 2018.)

An adverse reaction to medication is defined by the WHO (World Health Organization) as an unintentional injury that occurs during the use of a medication used in the usual therapeutic doses for treatment, prophylaxis or diagnosis. (Emerick et al., 2015) In this sense, pharmacodermias are skin and/or mucosal diseases that can become systemic, triggered directly or indirectly by the use of medications.

Drug reactions can be triggered by immunological mechanisms, known as drug allergies, but they can also be caused by non-immunological mechanisms. In general, there are four types of hypersensitivity described, three of which are related to humoral immunity and one to cellular immunity (Azulay et al., 2022).

Currently, Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are considered to be opposite spectrums of the same disease, epidermal necrolysis. The differentiation between the two diseases is basically clinical: in SJS the detachment from the body surface is less than 10% and in TEN the detachment corresponds to more than 30% of the body surface (Campos et al., 2024).

The treatment of these pharmacodermias is the same, with hospitalization of the patient being necessary, in the ICU (Intensive Care Unit), in addition to isolation to prevent infection and avoid contact with drugs present in the environment. Medications previously used by the patient should be withdrawn immediately, and the most important step is maintaining the patient's water and electrolyte balance (Evandro; Rivitti, 2018).

OBJECTIVES

The aim of this study is to list the clinical characteristics of Stevens Johnson Syndrome and Toxic Epidermal Necrolysis, differentiating between the two pharmacodermias and analyzing their possible therapeutic approaches.

METHODOLOGY

The methodology chosen was a literature review, in the form of a systematic review, based on the study of references already analyzed and ratified by written and electronic means.

The study consists of a bibliographic survey of databases on the Google Scholar platform, the Ministry of Health, the Brazilian Society of Dermatology, the World Health Organization, as well as Dermatology textbooks, selecting only materials published between 2015 and 2022, worldwide, in Portuguese and English. The following keywords were used in Portuguese: Dermatology, Stevens-Johnson Syndrome, Common Tegument and Drug Hypersensitivity Syndrome. The survey generated 18 articles, 7 of which were deemed pertinent to this study.

Inclusion criteria: original studies, whether prospective or retrospective, and literature reviews that address drug reactions with the development of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis. Exclusion criteria: outdated studies, from years before 2015 and in languages other than English and Portuguese.

RESULTS AND DISCUSSION

IMMUNOPATHOLOGY OF PHARMACODERMA

Drug reactions can be triggered by immunological mechanisms, known as drug allergies, but they can also be caused by non-immunological mechanisms. In general, there are four types of hypersensitivity described, three of which are related to humoral immunity and one to cellular immunity (Azulay et al., 2022).

The first type of hypersensitivity is type 1, anaphylactic or immediate, this can be produced by analgesics, serums or penicillins, it is dependent on antibodies of the IgE class, releasing vasoactive substances of histamine, bradykinin, leukotrienes, platelet activating factor, tryptase and prostaglandins, which can be triggered in seconds, being fatal. (Neto et al., 2019).

Cytotoxic hypersensitivity is the second type of reaction, in which there is an antigenic determinant attached to the cell surface and IgG or IgM, and after the antigen-antibody union, the target cell is destroyed. This sensitivity has been found in cases of thrombocytopenic purpura, Graves' disease, Goodpasture's syndrome, among others. Type 3 sensitivity is mediated by immune complexes and has been frequent in serum sickness caused by penicillin (Evandro; Rivitti, 2018).

In the case of SSJ and NET, the hypersensitivity present is type 4, or late cellular, an immunolo2gical mechanism that occurs through the sensitization of T lymphocytes to a protein antigen or hapten (Aliezsa et al., 2020).

In addition, cross-reactions can occur when different drugs share the same radical, for example, sulfa and phenolphthalein share the paraphenylenediamine ring (Campos et al., 2023).

As for the genetic association of pharmacodermias, there is no certainty as to the possible susceptibility of some people. However, some genes from the HLA-B family have been associated with reactions caused by some specific drugs, such as: HLA-B*1502, associated with the use of carbamazepine and sulfa drugs, HLA-B*3801 with lamotrigine, HLA-B*5901 with metazolamide, HLA-B*7301 with NSAIDs from the oxycans category, HLAB*3802 with sulphamethoxazole (Azulay et al., 2022).

STEVENS JOHNSON SYNDROME

Currently, Stevens Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are considered to be opposite spectrums of the same disease, epidermal necrolysis. The differentiation between the two diseases is basically clinical: in SJS the detachment from the body surface is less than 10% and in TEN the detachment corresponds to more than 30% of the body surface (Campos et al., 2024).

The drugs often responsible for producing this syndrome are sulfa drugs, anticonvulsants and NSAIDs. The most common anticonvulsants are diphenylhydantoin and barbiturates. Antibiotics can participate in the pathogenesis of JSS, but less frequently (Ferreira et al., 2020).

Generally, the clinical manifestations are preceded by an infection, making it difficult to understand whether the cause of the syndrome is the infection or the drugs, or a synergism between the two. Prodromal signs of infection appear even before integumentary lesions, such as fever, headache, runny nose, myalgias, arthralgias, which can last up to 2 weeks (Evandro; Rivitti, 2018).

The clinical presentation of JSS is characterized by multiple cutaneous-mucosal involvement, with the mouth being the affected area, with lesions on the lips, tongue and oral mucosa. Hemorrhagic or purulent blisters may also appear, which when ruptured leave erosive areas covered in crusts (Caminha et al., 2021).

The eyes are often affected, with lesions on the eyelids, serous, catarrhal or purulent conjunctivitis, anterior uveitis, corneal lesions and panophthalmos. In addition to the eyes, other mucous membranes can be affected, such as the anal and genital mucosa, with urethritis, balanitis and vulvovaginitis (Azulay et al., 2022).

TOXIC EPIDERMAL NECROLYSIS

NET is an extremely serious and often fatal bullous disorder triggered by drugs, infections and other non-determining factors. Drugs are the main causative agents of the syndrome, including: sulfonamides, NSAIDs, pyrazolone derivatives, dipyrone, phenylbutazone, allopurinol, anticonvulsants, cephalosporins, corticosteroids and antineoplastics (Azulay et al., 2022).

In addition to drugs, there may be triggering causes, such as viral infections, vaccinations, radiotherapy, lymphomas, graft-versus-host disease and HIV infection (Dimri et al., 2016).

The full-blown rash is preceded by a prodromal phase of varying duration. This phase is characterized by general malaise, fever, cutaneous hypersensitivity accompanied by superficial inflammation of the conjunctivae, eyelids, oropharynx and genitals (Campos et al., 2024).

The rash begins with erythema in the large skin folds, followed by explosive necrosis of the skin. Serohaemorrhagic flaccid blisters form with the detachment of extensive epidermal flaps along the entire skin surface, leading to the appearance of a large burn (Aliezsa et al., 2020).

Nikolsky's sign is the main differentiator between SSJ and NET, used to assess the amount of skin detachment present in the patient. The semiological sign is performed by pressing the lesion with the finger or a blunt object to see if there is displacement of the epidermis (Evandro; Rivitti, 2018).

Patients develop mucosal lesions, high fever and intense toxemia alongside the appearance of blisters. Visceral lesions, tracheitis, bronchopneumonitis, gastrointestinal bleeding, glomerulonephritis and acute tubular necrosis. Deaths are usually due to sepsis or DIC (Disseminated Intravascular Coagulation). (Caminha et al., 2021)

THERAPEUTIC APPROACHES AND PROGNOSTIC FACTORS

In cases of major burns, SSJ and NET, the SCORTEN (SCORE of Toxic Epidermal Necrosis) severity score can be used, which is considered an important predictor of prognosis. A SCORTEN score of 0 to 1 equals 3.2% mortality, 2 points equals 12.1% mortality, a score of 3 equals 35.3% mortality, 4 points equals 58.3% and if greater than or equal to 5 the mortality rate corresponds to 90% (Evandro; Rivitti, 2018).

SCORTEN considers certain factors to be closely related to the mortality and morbidity of affected patients: age greater than or equal to 40 years, tachycardia (120 beats per minute), malignancy, detached surface greater than 10%, urea greater than 28 mg/mL, glycemia greater than 252 mg/ML and sodium bicarbonate less than 20 mmol/L (Azulay et al., 2022).

The treatment of these pharmacodermias should be carried out in an Intensive Care Unit, requiring isolation to prevent infection and to avoid contact with drugs present in the environment. (Dimri et al., 2016)

It is important not to use any drugs on the patient in the ten days prior to the onset of the condition. Asepsis and maintaining water and electrolyte balance are the main pillars of treatment for this patient (Chopra et al., 2015).

Corticosteroids are not recommended as there is no solid evidence of clinical improvement; systemic antibiotics should be used in cases of infection. In NET specifically, patients benefit from the use of human immunoglobulin (0.2 to 0.75g/kg/day for 4 days), and plasmapheresis in very severe patients (Evandro; Rivitti, 2018).

CONCLUSION

It can be concluded, however, that when prescribing any medication, medical professionals should always bear in mind the possible adverse drug reactions that may occur. In addition, we must be prepared to treat the appearance of any adverse effect, including SSJ and NET dermatological emergencies.

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