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Clinical and Epidemiological Profile of Hypersensitivity Reactions to Medicines in Northern Brazil and Systematic Review

[1]Renan da Silva Bentes, [1, 2]Laila Sabino Garro,[3]Victor Luiz Ferreira, [3]Pedro Eduardo Alves da Silva, [3]Nelson Carlos Reis Filho, [3]Amanda Caetano de Sousa

1. Doctor, Federal Universityof Roraima, Boa Vista
2. PhD in Sciences from the University of São Paulo
3. Medical student at the Federal University of Roraima

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SUMMARY
Drug Hypersensitivity reactions (DHRs) account for 15% of all adverse drug reactions and affect 7% of the general population, whose most common clinical manifestations are dermatological. This is a cross-sectional, prospective study designed to assess the prevalence of DHRs in a reference hospital in the Far North of Brazil. In addition, a systematic review of studies on DHRs in Brazil was carried out, in which a total of 191 publications were obtained, in which 8 articles corresponded to the eligible number of 1.426 individuals, no corresponding one was carried out in the North Region of Brazil. In the current study, the prevalence rate of DHRs was 0.078% in the reference hospital where it was carried out, during a period of seven months.
Keywords: Drug hypersensitivity reaction; immediate drug hypersensitivity reaction; non-immediate drug hypersensitivity reaction
Acronyms: Acute Generalized Exanthematous Pustulosis: AGEP; Adverse Drug Reaction: ADR; DHRs non-immediate: DHR-N; DHRs immediate: DHR-I; Drug reaction with eosinophilia and systemic symptoms: DRESS; European Network for Drug Allergy: ENDA; Informed consent form: ICF; Maculopapular rashes: MPRs; Nonsteroidal anti-inflammatory drugs: NSAIDs; Stevens-Johnson Syndrome: SSJ; Toxic Epidermal Necrolysis: TEN.

I. INTRODUCTION

Adverse drug reactions (ADRs) are harmful and unintended effects after exposure to drug use. [1-3] In this scenario, drugs can produce reactions to the body due to immunological and non-immunological aspects, and hypersensitivity reactions to drugs (DHRs) correspond to 15% of all ADRs, thus affecting 7% of the general population, whose clinical manifestations the most common are dermatological ones with urticaria and maculopapular rash (MPR), which may also affect other physiological systems.[4-6]

DHRs can be immediate (DHR-I) or non-immediate (DHR-N). The first usually occurs between 1-6 hours after using the drug with a clinical picture of urticaria, angioedema, dyspnea, wheezing, anaphylaxis or anaphylactic shock, while the second groups cases such as vasculitis, toxic epidermal necrolysis (TEN), Stevens-Johnson Syndrome (SSJ), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Acute Generalized Exanthematous Pustulosis (AGEP).[7,8]

In Brazil, there have been few epidemiological studies with the aim of characterizing DHRs, as verified by searches in the medical literature on research platforms. Furthermore, the World Health Organization and the medical literature suggests the need for more pharmacovigilance services. [1,2,9] Thus, the present study aims to show the literary gap of DHRs in Brazil through the systematic review of cross-sectional epidemiological studies, as well as to expose original research with prevalence data carried out in the extreme North of Brazil, Roraima.

II. METHODOLOGY

1. Study Design

This is a cross-sectional, prospective study designed to assess the prevalence of DHRs in a reference hospital (tertiary level) in the Far North of Brazil (Hospital Geral de Roraima Rubens de Souza Bento), located in the city of Boa Vista- RR. And the duration of the study was seven months.

Regarding the systematic review, this consisted of a survey of cross-sectional articles, published nationally, complete, available, with no date limit, only in human beings, in individuals over eighteen years old, through the MEDLINE and LILACS platforms via BIREME (Latin

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American and Caribbean Center on Health Sciences Information) and PUBMED, using standardized terms from the DECS (Health Sciences Descriptors) platform.

In this context, according to the DECS platform and with descriptors in Portuguese and English, the following terms were selected: "Cross-Sectional Studies and Drug Hypersensitivity and Brazil"; "Prevalence and drug hypersensitivity and Brazil" ("Prevalence and Drug Hypersensitivity and Brazil"); "Observational Study and Drug Hypersensitivity and Brazil".

In addition, because the articles in the journal of the Brazilian Association of Allergy and Immunology (ASBAI), Latin American Society of Allergy, Asthma and Immunology (SLAAI) are indexed in the LILACS platform, one can infer greater reliability in the collection of epidemiological data about of the concomitant theme DHR and prevalence, since such a platform was explored in terms of bibliographic analysis. In addition, this systematic review was designed with the aim of providing a theoretical basis and comparing data from the literature with the present epidemiological study.

Articles with methodology of the types were excluded for the systematic review analysis: case report or case series, systematic review, meta-analysis, longitudinal and randomized controlled clinical trials, as the intention was to promote the present work with the selection of articles with the same research design carried out in the data collection through a specific questionnaire.

Studies approaching individuals younger than 18 years of age were excluded, as the objective was to elucidate the epidemiological profile of the adult population.

In addition, non-Brazilian studies were excluded from the selection of the systematic review to clarify the Brazilian national scenario of prevalence in DHRs.

The flowchart (figure 1) demonstrates these stages of the methodological process. In addition, the publications raised through the selection of the systematic review were summarized in table 1.

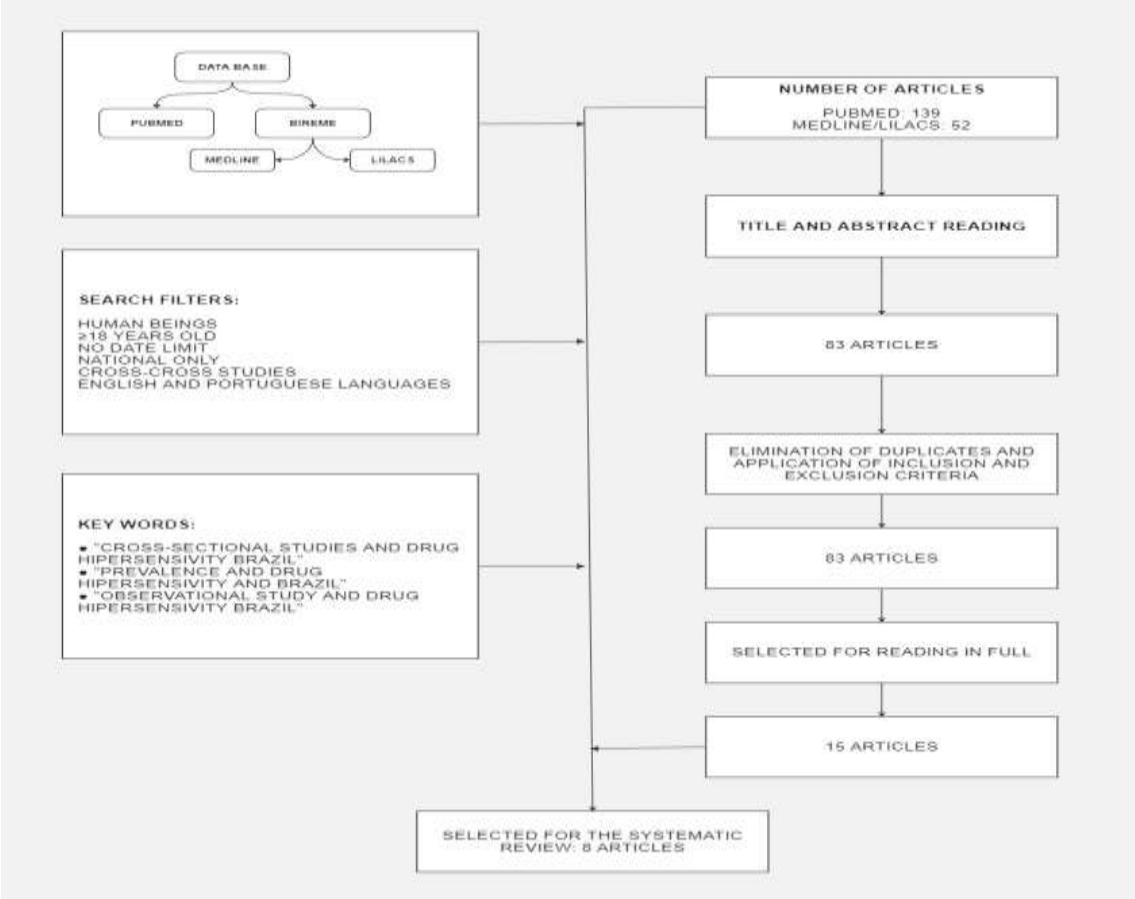

Figure 1. Flowchart that summarizes the format used for the selection of articles used in the systematic review whose number of articles corresponded to eight publications.

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2. Population

Roraima is a state in the extreme north of the Brazilian Legal Amazon and has a population of around 636.000 inhabitants, according to a census carried out by the Brazilian Institute of Geography and Statistics (IBGE) in 2022, making it the least populous state in the country.[10]

It is a state characterized by two international borders, Venezuela and French Guiana, as it is home to the largest indigenous village population in Brazil, corresponding to 15% of the total population of the state of Roraima.[11]

The research was carried out at the Roraima General Hospital in Boa Vista (main city), being the only reference hospital and tertiary health care service in the state, so that all critically ill patients at the state level are allocated in this center.

The research took place from October 1, 2021, to April 30, 2022. During this period, visits were daily to the clinical and surgical wards and intensive care units for an active search for patients with suspected DHRs. Drugs suspected of causing DHRs were identified according to the clinical suspicion of the teams responsible for the cases.

3. Sample and Sampling

About data collection, the overall prevalence of DHRs at the Hospital Geral de Roraima was statistically determined based on a 95% confidence index (CI=95%), "p" value <0.05 and a maximum error of 5%, according to simple random sampling. Thus, using the Gaussian curve and using the critical value of 1.96 and an estimated minimum prevalence of hospitalized patients with DHR of 1%, the sample size (N) for the present study corresponded approximately to approximately 15 patients. Despite efforts, only four patients with DHR were found.

4. Search Procedure

Patients were admitted to the research after being invited to participate in the research after signing the informed consent form (ICF) and, after that, the researchers applied a standardized questionnaire for DHRs from the European Network for Drug Allergy (ENDA).[12]

5. Inclusion and Exclusion Criteria

Inclusion criteria consisted of individuals over 18 years of age, both male and female, hospitalized, including individuals from intensive care units, with a minimum hospitalization time of 24 hours and cognitive capacity of the patient and/or legal caregiver. to answer the questionnaire and sign the ICF.

Exclusion criteria in this study were patients who met at least one of the requirements: under 18 years of age; hospitalization for less than 24 hours; indigenous; foreigners (because we sought to acquire national data); same patient with new hospitalization; patient and/or legal caregiver without cognitive capacity to sign the ICF.

6. Data Analysis

Each participant's data were stored and analyzed in Microsoft® Excel® for Microsoft 365 MSO (Version 2307 Build 16.0.16626.20086) 64 bits, in which descriptive analysis of the participants' data was performed.

7. Ethical Aspects

The study was approved by the Ethics Committee in Research involving human beings of the Federal University of Roraima (UFRR) - Certificate of Presentation of Ethical Appreciation number 12805319.0.0000.5302.

III. RESULTS AND DISCUSSION

According to the appropriate and standardized terms, a total of 191 articles were obtained and after applying the inclusion and exclusion criteria, 83 publications were captured. After proper reading of the abstract and elimination of duplicates, 15 articles were selected for reading in full, with 8 being eligible for this systematic review.

Authors	StudyOutcome	Sample SizeandTemporality	BrazilianStateofStudy
Luis Felipe C. E. and collaborators (2010)	The prevalence of self-reported DHR was 12.11%	1.015 (prospective)	São Paulo
Luana Bernardes A. and collaborators (2017)	They found a rate of SSJ and TEN of 43% in individuals aged over 20 years	86 (retrospective)	Distrito Federal

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Mariane Ferreira B. E. and collaborators (2014)	The most implicated drugs were anticonvulsants (45.45%) and antibiotics (13.63%)	22 (retrospective)	Distrito Federal
Mayumi Ueta andcollaborators (2014)	Significant association between SSJ/TEN and the HLA-B*44:03 allele	39 (prospective)	São Paulo
Luciana Rosa G. andcollaborators (2014)	They verified a severe skin reaction (SSJ, TEN, DRESS and PEGA) in 3,048 hospitalized patients, out of a total of 173.767 hospitalized	37 (retrospective)	Rio Grande do Sul
Rosana Câmara A. andcollaborators (2020)	High prevalence of urticaria (32.9%) associated with dipyrone-induced DHR	73 (retrospective)	São Paulo
Luis Felipe E. and collaborators (2019)	Gene segregation analysis of the COX/5-LO pathway did not reveal any variants of biological importance	4 (prospective)	São Paulo
Patricia Guerzet A.B. and collaborators (2019)	Confirmed anaphylaxis was associated with DHR in about 13% of the analyzed sample	150 (retrospective)	São Paulo

Table 1. Systematic Review Summary.

Table 1. Above is the outcome found by each cross-sectional study and the respective sample size, according to the compilation of articles from the systematic review proposed in the methodology of this article to complement the theoretical basis carried out in this epidemiological study in the municipality of Boa Vista, Roraima, Brazil. A total of 1.426 individuals were analyzed. Legend: Toxic Epidermal Necrolysis: TEN; Acute Generalized Exanthematic Pustulosis: AGEP; Drug Hypersensitivity Reaction: DHR; Stevens-Johnson Syndrome: SSJ; Drug Hypersensitivity Syndrome (also called Drug Reaction with Eosinophilia and Systemic Symptoms): DRESS.

Regarding the systematic review of Brazilian studies, Luis Felipe C. E. and collaborators (2010)[13] prospectively verified the prevalence of DHR in a sample of 1.015 university students, using a self-administered questionnaire, in which the drugs most involved were anti-inflammatory drugsnon-steroidal inflammatory drugs (NSAIDs) (45.9%), in addition to beta-lactam antibiotics and sulfonamides (25.40%) and the dermatological condition was the most reported (N=99). Furthermore, Luana Bernardes A. et al. (2017)[14] analyzed from 1999 to 2014 the rate of patients with SSJ and TEN in public hospitals in the Federal District, verifying an N=37 in individuals aged over 20 years among patients aged 0-80 years old.

Mariane Ferreira B. E. and collaborators (2014)[15] described aspects of SSJ and TEN from 2007-2012 with a rate of DHR of 22 patients, in which the most implicated drugs were anticonvulsants with 45.45% (N=10) followed by antibiotics 13.63% (N=3). The number of patients diagnosed with TEN and SSJ were 9 and 7, respectively. In another study with a similar theme, Mayumi Ueta et al. (2014)[16], when conducting a genetic study of a sample of 39 brazilians patients with severe complications of the ocular surface, found a significant association between SSJ/TEN and the HLA-B*44:03 allelewhen compared with 134 healthy patients.

DHR-N were evaluated by Luciana Rosa G, et al. (2014)[17] in severe skin reactions to drugs in a tertiary hospital between the years 2005-2010, in which they verified the occurrence of 1 in 3.048 hospitalized patients, in a total of 173.767 admitted. In this scenario, the most involved drugs were anticonvulsants (40.4%), antibiotics (26.3%) and analgesics/anti-inflammatories (10.5%). In addition, DRESS was the most frequent when compared to SSJ, TEN and AGEP.

Rosana Câmara A. et al. (2020)[18] when characterizing the phenotype of patients with

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aspirin-exacerbated respiratory disease (AERD) in a sample of 73 patients, in which they noted a high prevalence of urticaria (32.9%) associated with dipyrone-induced DHR.In another research of a genetic nature, Luis Felipe E. and collaborators (2019)[19] studied genetic markers in order to elucidate a hypersensitivity relationship in patients with isolated angioedema induced by non-steroidal anti-inflammatory drugs (NSAIDs) in four individuals and their respective families, in which the gene segregation analysis of the COX/5-LO pathway did not reveal any variant of biological relevance.

With regard to DHR-I, Patricia Guerzet A. B. and collaborators (2019)[20] analyzed a sample of 150 patients, of which 13% (N=43) were associated with DHRs and of these, a total of 32 patients were adults.

As for the data from the data collection study carried out in the extreme north of Brazil, this took place over a period of seven months, with a total of 5.159 patients hospitalized during this period. In addition, an N=4 of patients with DHR was found, so the prevalence of patients with DHR at the Roraima General Hospital corresponded to 4/5,159, that is, approximately 0.078%, with 75% composed of DHR-N. Data for each patient are summarized in table 2.

Profile ofIncludedPatients	Diagnostics	Suspected drug	Clinical Manifestations	Treatment	DHR Type	Sex	Age (years)
Patient 1	CAP complicatedwith ARF	Dipyrone	MPRgeneralized	drugsuspension	late	Man	58
Patient 2	CAP; HF; ESAH; DM; CKDinRRT	Teicoplanin	MPRgeneralized	drugsuspension	late	Man	75
Patient 3	Inflammatoryacuteabdomen	iodinecontrast	Urticaria, nausea, vomitinganddiaphoresis	Iodine contrast not used later; corticosteroid	immediate	Woman	23
Patient 4	pituitary tumor	carbamazepine	Feeling of fear, panic, dry cough, diaphoresis, MPR generalized	drugsuspension	late	Woman	35

Table 2. Characteristics of each patient with DHR with data collection.

Legend. DM: diabetes mellitus; CKD: chronic kidney disease; MPR: maculopapular rash; ESAH: essential systemic arterial hypertension; DHR: drug hypersensitivity reactions; HF: heart failure; ARF: acute respiratory failure; CAP: community-acquired pneumonia; RRT: renal replacement therapy.

It was found that MPR was the manifestation of DHR-N in all cases, which is consistent with the data presented in the literature, as Pirmoham M. et al. (2011)[21] found that the skin was the most often affected in non-immediate reactions. Data that corroborate the results of the current research, given that 75% of the patients found had DHR-N, with the small sample found as a limitation.

The prevalence found deserves to have some characteristics mentioned.First, there is no pharmacovigilance service at the collection unit, whereas all cases were identified by active search by investigators during daily visits, so patients with DHRs may have been missed during the study. And, due to this reason, the prevalence rate of 0.078% found in this study may be an underestimate.

Second, because the present study is cross-sectional, it does not allow extrapolations, being only a punctual epidemiological evaluation. Nevertheless, this research is presented as the first carried out in the state of Roraima, as well as in the North Region of Brazil, since no studies with a similar methodological character were found in the

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systematic review carried out concomitantly with this publication.

The reaction presented to iodine was consistent with the literature, as it corresponded to anDHR-I, a clinical condition that must be identified and present immediate intervention.[22, 23]

Thus, the work carried out reinforces the need for a drug pharmacovigilance service at the state level and further studies of epidemiological characterization in the Northern Region of Brazil. In addition, this was reinforced by the systematic review carried out and summarized in the table, in which of the five geographic regions of Brazil, most of the studies found were in the Southeast Region and none were found in the North and Northeast regions, demonstrating a relevant scientific gap in the literature.

Thus, Xinling Li and collaborators (2018)[24] point out that the implementation of rapid communication through reports and automation through electronic records in reference hospitals, as well as association with research centers, is an important pharmacovigilance notification tool. Demoly et al. (2014),[9] also point out that such tools are scarce and, therefore, require further studies. Thus, the present work has the merit of being the first work approaching DHR in the North Region of Brazil, since according to a systematic review carried out and exposed in this publication of a total of 1.426 individuals analyzed in Brazilian studies, none corresponding to this geographic region was found.

IV. CONCLUSION

A prevalence rate of 4/5.159 was found, that is, approximately 0.078% for DHRs in a reference hospital in the extreme North of Brazil in a period of seven months of study. It becomes imperative to implement a local pharmacovigilance service to minimize underreporting and improve intervention and prevention measures, in addition to more research at the regional level.

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