Complications of herpes zoster hospitalizations in a reference hospital in Fortaleza-Ceará, 2009-2018

Complicações de internações por herpes zoster em um hospital de referência em Fortaleza-Ceará, 2009-2018

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Abstract

Objective: the aim of this study was to relate sociodemographic, epidemiological and clinical conditions to the occurrence of severe cases of HZ in reference hospital of Fortaleza. Methods: this is a cross-sectional analytical study, based on medical records of patients admitted from 2009 to 2018. Pearson’s x² test or Fisher’s exact test were used when appropriate. Results: we analyzed 196 medical records. The presence of complications occurred in 69.9%, the most affected region was the cranial (68.9%), and 1.5% died. The presence of vesicles (PR=1.37; 95%CI: 1.03-1.82; p=0.01) and the choice of antibiotic associated antiviral therapy (PR=0.58; 95%CI: 0.46-0.73; p=0.00) were significantly associated with the severity. Conclusions: the disease may be more severe at ages over 50. The presence of lesions in vesicles was associated with a higher prevalence of complications and the use of antibiotics and antivirals as a protective factor.

Keywords: Herpes zoster; Varicella Zoster Virus Infection; Epidemiology; Risk factors.

INTRODUCTION

Herpes Zoster (HZ) is an infectious disease caused by the reactivation of primary infection by the VZV. Some symptoms, such as pain, itching, or tingling, appear before the appearance of a skin lesion at the reactivation site. In almost all cases, HZ causes a painful rash that completely disappears in 2 to 4 weeks¹.

During primary infection, VZV infects sensory nerve cells through retrograde axonal transport, going to the dorsal root ganglia near the spinal column or due to viremia of infected T cells, establishing latency for an indefinite period².

Otherwise, if the immune system declines, the VZV is reactivated and, through antrograde transport, proceeds to the sensory cutaneous nerves causing a painful unilateral eruption along the dermatome, mainly in the thoracic, cranial, cervical, or lumbar regions³.

There are two types of vaccine, one that has the live attenuated virus, with 70% protection effectiveness and another non-living subunit recombinant vaccine, that has 90% effectiveness, and can be administered to immunocompromised individuals⁴. In Brazil, there is a live attenuated virus vaccine that prevents HZ, however, it is only available in the private health network and at a relatively high cost, approximately US$ 125.00, limiting access to almost all the population that depends on the public health system⁶.

HZ incidence coefficients in North America, Europe, and Asia range from 3 to 5 cases per 1,000 person-years. These values tend to increase as the age grows and, in individuals over 70 years old, the incidence ranges more than double and became
Complications associated with HZ can be: cutaneous, such as bacterial skin infections; ophthalmological problems, such as decreased visual acuity, keratitis, uveitis, and progressive retinal necrosis; neurological disorders such as post-herpetic neuralgia (PHN), facial paralysis, meningitis, uveitis, and even cerebellitis; pulmonary complications such as pneumonia may still appear; liver diseases such as hepatitis; cardiac disorders such as myocarditis, pericarditis or even cause myocardial infarction.

Besides all these complications, HZ is not a compulsory notification disease in Brazil, and few studies show the characteristics of hospitalized cases of HZ and the factors associated with its main complications. Thus, this study aimed to describe clinical and epidemiological characteristics and explore the association between these factors and complications in hospitalized HZ disease at an infectious diseases reference hospital.

METHODS

Study design

This is a cross-sectional analytical study based on medical records of patients from Fortaleza city who were hospitalized by HZ between the years 2009 to 2018 at an infectious diseases reference hospital, located in the city of Fortaleza in the state of Ceará, Brazil, and that has not been transferred to other units.

The local of study is a public hospital of the Health Department of the Ceará State, recognized as the reference in the treatment of infectious diseases and a teaching hospital, accredited by the Ministries of Health and Education with a medical residency in infectious diseases, as well as a multi-professional residency.

Case definition: A severe case of HZ was defined as a patient who had any kind of complication associated with the condition, namely: cutaneous, cardiac, liver, neurological, respiratory complications, genitourinary alterations, or any other alteration observed.

Independent variables: The independent variables were divided into sociodemographic; epidemiological and clinical aspects corresponding to evolution, laboratory data, and treatment.

HIV-positive individuals were classified as immunodeficiency. In chronic disease, we highlight diabetes, cancer, asthma, kidney diseases, neuropsychiatric diseases, and cardiovascular diseases. The variable "Go to the doctor" was considered every time the individual looked for medical attention until admission. For the clinical aspects and evolution, we looked for variables such as the period of hospitalization, time living with HZ, characteristics of the HZ lesions, location of the HZ lesions, type of HZ lesions, development of a complication, the type of complication, as well as the number of complications. Other variables also were used in this study: the presence of fever, need for intensive care, hematological changes, the evolution of the case (discharge or death), and the type of therapy used. The variable time living with HZ was the time in days from the HZ diagnosis until the hospitalization by HZ.

The relevant changes in the hemogram exam were observed and anemia was classified as a reduction in blood hemoglobin rate lower than expected. Thrombocytopenia was classified as a reduction in the number of platelets compared to reference values. They were included in “other changes” such as thrombocytosis (higher than expected platelet count), neutropenia (reduced neutrophil count in the blood), leukocytosis (increased number of leukocytes), and any other relevant changes found.

Statistical analysis

The collected data were stored in the Epi InfoTM version 7.2 program (CDC, Center for control of diseases and Prevention) for later statistical analysis.

Stata version 15.1 (StataCorp, College Station, Texas, USA) was used for statistical analysis. Initially, we calculated the relative frequencies of each qualitative variable and the central trend measures for quantitative variables. Then, a bivariate analysis was carried out with the presence of clinical complications as the outcome variable. Each group of characteristics: sociodemographic, epidemiological, and clinical, were related to the development of complications, to identify any associated factors for the presence of clinical complication.

The results were presented in tables and figures. An error of 5% was assumed and Pearson's Chi-square test or Fisher's exact test were used when appropriate. The prevalence ratio was calculated as well as its 95% confidence interval.

We also performed a spatial distribution of the neighborhood of residence of all those cases. We created thematic maps in ArcMap version 9.2 software (Environmental Systems Research Institute -ESRI, Redlands, CA, USA).

The study was submitted to and approved by the SJH ethics and research committee in Fortaleza-CE, under number 3.106.633.

RESULTS

A total of 367 medical records were found during the study, but only 248 hospitalization records were distributed between 2009 and 2018. Of these, it was possible to collect data in 196 (79.0%) of the records, the other ones were not found in the Sector of
Medical and Statistics Archive of the hospital (Figure 1).

Figure 1. Sample selection process of the medical records during the research.

The year 2011 had the highest number of hospitalizations with 15.7%. From 2012 to 2015, the number of cases remained between 20 to 25 per year, and only in 2016 increased to 31 (12.5%) and decreased in the following years (Figure 2).

Figure 2. Distribution of the number of medical records per HZ hospitalized in the SJH in Fortaleza-CE, 2009-2018.

HZ hospitalized patients were most frequently male (52.0%), had an active occupation in the labor market (27.5%), and were in elementary school (39.0%). The median age of these patients was 43 years, with an interquartile range of 22 to 65 years. The largest number of hospitalizations occurred in the age group above 50 years (42.3%).

The pilgrimage for medical care was also described so that 53.1% of the affected individuals looked for medical care more than once for the complete resolution of their condition. The median time from disease progression to medical demand was 5 days, with an interquartile range from 4 to 7 days. The period of hospitalization had a median of 7 days and an interquartile range of 5 to 8.5 days. The presence of factors that could worsen the condition was 58.0%. Of these, 34.0% had some type of chronic disease, another 21.0% had HIV infection. About 1.0% of the pregnant women were affected by the reactivation of the VZV. Of the HZ hospitalizations, about 70.0% had some type of complication associated with the condition. A total of 16.0% of patients had more than one type of complication. The most common complications were cutaneous (50.0%) and neurological (16.8%). The cutaneous complications observed were bacterial infections (55.1%), cellulitis (33.7%), atypical lesions (6.1%), and edema (5.1%). As for neurological, neuralgia occurred in 75.8%, headache (15.1%), and other neurological manifestations (9.1%).

Hematological changes were observed in 57 people (38.0%), and in 30 of them (20.0%) there was a decrease in platelet count. The situation was extreme for 3.0% of patients, leading to the need for intensive care. Of the studied hospitalizations, 1.5% died (Table 1).

Table 1. Characteristics of hospitalizations for HZ in the SJH in Fortaleza-CE, 2009-2018.

| Variables              | n  | %  |
|------------------------|----|----|
| **Sociodemographic**   |    |    |
| Sex                    |    |    |
| Male                   | 102| 52,04|
| Female                 | 94 | 47,96|
| Age group (in years)   |    |    |
| 1-10                   | 18 | 9,18|
| 11-20                  | 28 | 14,29|
| 21-30                  | 22 | 11,22|
| 31-40                  | 26 | 13,27|
| 41-50                  | 19 | 9,69|
| >50                    | 83 | 42,35|
| Schooling              |    |    |
| Illiterate             | 11 | 5,64|
| Elementary School      | 76 | 38,97|
| High school            | 36 | 18,46|
| University education   | 5  | 2,56|
| Ignored                | 67 | 34,36|
| Occupation             |    |    |
| Active                 | 54 | 27,55|
| Retired                | 47 | 23,98|
| Unemployed             | 14 | 7,14|
| From Home              | 12 | 6,12|
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| Variables                          | n  | %   |
|------------------------------------|----|-----|
| Student                            | 38 | 1,39|
| Ignored                            | 31 | 15,82|

**Epidemiological**

| Visits to the doctor | n  | %   |
|----------------------|----|-----|
| 1                    | 92 | 46,94|
| 2                    | 92 | 46,94|
| 3                    | 4  | 4,59 |
| 4                    | 3  | 1,53 |

**Risk factors**

| No                  | 83 | 42,35|
|---------------------|----|-----|
| Yes                 | 113| 57,65|

**Types of risk factors**

| Immunodeficiency   | 42 | 21,43|
|---------------------|----|-----|
| Chronic disease     | 67 | 34,18|
| Pregnant            | 2  | 1,02 |
| Transplanted        | 1  | 0,51 |

**Clinics and evolution**

**Characteristics of injuries**

| Disseminated    | 22 | 11,22|
|-----------------|----|-----|
| Place           | 174| 88,78|

**Types of injuries**

| Stains          | 2  | 1,04 |
|-----------------|----|-----|
| Papules         | 24 | 11,44|
| Vesicles        | 149| 77,20|
| Pustules        | 18 | 9,33 |
| Crust           | 20 | 10,36|

**Reactivation region**

| Cervical        | 3  | 1,72 |
|-----------------|----|-----|
| Cranial         | 120| 68,97|
| Dorsal          | 4  | 2,30 |
| Thoracic        | 23 | 13,22|
| Other *         | 24 | 13,79|

**Fever**

| No                | 94 | 48,21|
|-------------------|----|-----|
| Yes               | 101| 51,79|

**Complication**

| No                | 59 | 30,10|
|-------------------|----|-----|
| Yes               | 137| 69,90|

**Number of complications**

| 1                 | 105| 53,57|
|-------------------|----|-----|
| 2                 | 25 | 12,76|
| 3                 | 5  | 2,55 |
| 4                 | 1  | 0,51 |

**Types of complications**

| Cutaneous         | 98 | 50,00|
|-------------------|----|-----|
| Respiratory       | 9  | 4,59 |
| Neurological      | 33 | 16,84|
| Cardiac           | 1  | 0,51 |
| Hepatic           | 3  | 1,53 |
| Genitourinary     | 4  | 2,05 |
| Other**           | 27 | 13,78|

**Types of hematological changes**

| Anemia            | 30 | 20,00|
|-------------------|----|-----|
| Thrombocytopenia  | 30 | 20,00|
| Thrombocytosis    | 1  | 0,67 |
| Other***          | 4  | 2,67 |

**Intensive Care Unit (ICU)**

| No                | 190| 96,94|
|-------------------|----|-----|
| Yes               | 6  | 3,06 |

**Outcome**

| Cure              | 193| 98,47|
|-------------------|----|-----|
| Death             | 3  | 1,53 |

* Flank, lumbar, upper limbs, lower limbs, inguinal region, thighs, buttocks;
** Conjunctivitis, decreased visual acuity, blurred vision, otalgia, otitis, disseminated HZ;
*** Eosinophilia, leukocytosis, monocytosis.

A total of 137 patients (70.0%) presented some type of complication associated with the HZ infection. There was no statistical difference between the prevalence of complications between the sexes (PR=0.93; 95%CI: 0.78-1.12; p=0.474), and likewise, the variables occupation and education, with p-values of 0.12 and 0.90, respectively.

The age group was significantly associated with the risk of having complications with advancing age, in particular, ages above 50 years old (PR=1.87; 95%CI: 1.10-3.16; p=0.00).

However, patients classified as retired had a 35% higher prevalence of complications than the active ones (95%CI: 1.07-1.68; p=0.12). There was no difference in the prevalence of complications in HIV-positive people, as well as in those with chronic disease or even in individuals who received an organ transplant.

In clinical characteristics, the presence of vesicles (PR:1.37; 95%CI: 1.03-1.82; p=0.01) and the choice of therapy with the use of antivirals associated with antibiotics conferred superior protection (PR:0.58; 95%CI: 0.46-.73; p=0.00).
## Table 2. Association between the presence of complications and independent variables of hospitalized cases of HZ in the SJH in Fortaleza-CE, 2009-2018.

| Variables                          | Total | Complications | %   | PR | C195% | p-value |
|------------------------------------|-------|---------------|-----|----|-------|---------|
| **Sociodemographic**               |       |               |     |    |       |         |
| Sex                                |       |               |     |    |       |         |
| Male                               | 102   | 69            | 67,65 | 3  | -     |         |
| Female                             | 94    | 68            | 72,34 | 0.93 | 0.78 – 1.12 | 0.474  |
| Age group (in years)               |       |               |     |    |       |         |
| 1-10                               | 18    | 8             | 44,44 | 1  | -     |         |
| 11-20                              | 28    | 21            | 75,00 | 1.68 | 0.96 – 2.95 |         |
| 21-30                              | 22    | 14            | 63,64 | 1.43 | 0.78 – 2.62 |         |
| 31-40                              | 26    | 12            | 46,15 | 1.03 | 0.53 – 2.01 |         |
| 41-50                              | 19    | 13            | 68,42 | 1.53 | 0.84 – 2.80 |         |
| >50                                | 83    | 69            | 83,13 | 1.87 | 1.10 – 3.16 | 0.001  |
| Occupation                         |       |               |     |    |       |         |
| Active                             | 54    | 35            | 64,81 | 1  | -     |         |
| Retired                            | 47    | 41            | 87,23 | 1.35 | 1.07 – 1.68 |         |
| Unemployed                         | 14    | 11            | 78,57 | 1.21 | 0.86 – 1.69 |         |
| From Home                          | 12    | 8             | 66,67 | 1.02 | 0.65 – 1.60 |         |
| Student                            | 38    | 27            | 71,05 | 1.09 | 0.82 – 1.45 | 0.121  |
| Schooling                          |       |               |     |    |       |         |
| Illiterate                         | 11    | 7             | 63,64 | 1  | -     |         |
| Elementary school                  | 76    | 55            | 72,37 | 1.13 | 0.71 – 1.81 |         |
| High school                        | 36    | 25            | 69,44 | 1.09 | 0.66 – 1.79 |         |
| University education               | 5     | 4             | 80,00 | 1.25 | 0.67 – 1.35 | 0.907  |
| Epidemiological                    |       |               |     |    |       |         |
| Immunodeficiency                   |       |               |     |    |       |         |
| No                                 | 154   | 109           | 70,78 | 1  | -     |         |
| Yes                                | 42    | 28            | 66,67 | 0.94 | 0.74 – 1.19 | 0.607  |
| Chronic disease                    |       |               |     |    |       |         |
| No                                 | 129   | 89            | 68,99 | 1  | -     |         |
| Yes                                | 67    | 48            | 71,64 | 1.03 | 0.86 – 1.26 | 0.701  |
| Transplanted                       |       |               |     |    |       |         |
| No                                 | 195   | 136           | 69,74 | 1  | -     |         |
| Yes                                | 1     | 1             | 100,0 | 1.43 | 1.30 – 1.57 | 1.000  |
| Clinics and evolution              |       |               |     |    |       |         |
| Vesicles                           |       |               |     |    |       |         |
| No                                 | 44    | 24            | 54,55 | 1  | -     |         |
| Yes                                | 149   | 111           | 74,50 | 1.37 | 1.03 – 1.82 | 0.011  |
| Therapeutics used                  |       |               |     |    |       |         |
| Antiviral                          | 107   | 91            | 85,05 | 1  | -     |         |
| Antibiotic                         | 5     | 4             | 80,00 | 0.94 | 0.60 – 1.46 |         |
| Antiviral + antibiotic             | 84    | 42            | 50,00 | 0.58 | 0.46 – 0.73 | 0.000  |
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| Variables            | Total | Complications | %     | PR  | CI95%   | p-value |
|----------------------|-------|---------------|-------|-----|---------|---------|
| Haematological changes |       |               |       |     |         |         |
| No                   | 93    | 66            | 70,97 | 1   | -       |         |
| Yes                  | 57    | 39            | 68,42 | 0.96| 0.77 – 1.20| 0.741   |

Legend: PR - prevalence ratio; CI - Confidence interval; p-value - level of significance.

The spatial distribution of the neighborhood of residence of patients who were hospitalized for HZ encompasses about 63.8% (n = 76) of the neighborhoods of Fortaleza-CE. Some neighborhoods in the city located in the southwest (23.9%), west (19.9%), and southeast (19.4%) regions stood out with high hospital admissions. Thirty-two neighborhoods (27.0%) had only one hospitalization at the referral hospital over the study period (Figure 3).

**Figure 3.** Spatial distribution of the number of hospitalized patients for HZ in the SJH in Fortaleza-CE, 2009-2018.

**DISCUSSION**

This is the first study to investigate the factors associated with severity in the occurrence of hospitalizations for HZ in Fortaleza that is known. The complications of HZ are poorly studied and, consequently, epidemiological information is scarce. In our study, there was an association between the presence of complications and clinical factors, such as the presence of vesicles, and being over 50 years of age. In addition, there was an oscillation in the number of hospitalizations per HZ over the study period.

As a limitation of the study, we can highlight the lack of some medical records in the sector in some years. Some information needed to fill in the variables was either missing or incomplete, thus leading to a high number of ignored data. Another limitation is that this study was carried out in only one hospital in the capital. Thus, the present study represents a sample of HZ cases in Fortaleza.

The incidence of HZ tends to increase as the population ages increase\(^1\), this association may be due to the occurrence of immunosenescence, which is characterized by the natural decline of T-cell function as the age increases and consequent fall in response to VZV\(^2\), or manifests itself in people with weakened immune systems, usually due to health problems and the use of immunosuppressive drugs\(^3\). The risk of having PHN, which is a type of HZ complication, was also associated with age over 50, immunosuppression conditions, and comorbidities\(^4\).

In the literature, we did not find similar results that associated the presence of vesicles and the severity picture, however,
most cases of HZ happen with a cutaneous manifestation or the appearance of local infections and, in extreme cases, skin necrosis is possible. The same happened with therapy, but studies report that if started correctly and in time, it can decrease the severity of symptoms and avoid possible complications.

The southwest region of the city of Fortaleza is the most populous in the city, as well as the one with the lowest HDI, which justifies the largest number of visits, given that a large part of this population lives in conditions of extreme poverty, without access to basic health services. When it comes to presenting the signs and symptoms of HZ they already need specialized care. In some cases, for the diagnosis and treatment of HZ, the patient comes to seek medical attention more than once. Some studies report that individuals come to see the specialist more than 5 times.

Our study observed that the majority of those involved in the research had some factor that could worsen the condition, this finding corroborates with another study that reports that patients with underlying diseases are 1.8 to 8.4 times at risk of developing HZ. The presence of chronic diseases such as rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, chronic kidney disease, type 1 diabetes, depression, and even family history was associated with an increased risk of having HZ.

The cranial region showed the highest frequency of reactivation by the virus in our study. Infection rates in this region in other studies ranged from 11.5% to 14%. Reactivations of the virus in the cranial nerve, specifically the trigeminal nerve, can cause ophthalmic HZ and consequent ocular manifestations such as periorbital skin lesions, conjunctivitis, retinal necrosis, uveitis, and keratitis.

In some studies, the disseminated form of HZ has not been so reported, in our study just over 10% of the population had virus reactivation in more than one dermatome. In Argentina, this number was much higher, where 80% of patients admitted to the hospital with suspected disseminated HZ, 51.2% were confirmed.

The presence of complications occurred in almost 70% of the patients involved in this study, with just over 15% of these having more than one complication. This number was even higher compared to other studies. This can be explained by the greater number of hospitalizations with patients over 50 years old and with some risk factors that can decrease cell-mediated immune responses to VZV, and it is this decline that seems to explain the increased incidence and severity of HZ and its complications in the elderly.

Cutaneous complications in the study in question were the most recurrent, about half of those involved in the research had this type of complication. Secondary bacterial infection is usually caused by staphylococcal or streptococcal infections, and if not diagnosed in time can lead to septicemia.

The risk of PHN is associated with advanced age, severe acute pain, severe skin lesions, and patients with severe immunosuppression. The rates of patients who develop PHN after HZ range from 8.6% to 49.3%.

Complications observed in our study, such as: respiratory (pneumonia and respiratory failure), as well as hepatic (hepatitis) and complications in the genitourinary system (urinary tract infection - UTI or renal failure), are rarely reported in studies, but associated complications are possible to HZ in adults or children.

The presence of cardiac complications was observed in only one patient with changes in heart rate. Other studies have observed a 1.2 to 1.7-fold increase in the risk of myocardial infarction one week or months after the diagnosis of HZ.

The types of hematological changes were the same as those observed in another study conducted in Argentina, but the highest frequency occurred in thrombocytopenia, followed by leukopenia, these types of hematological changes are frequent in patients affected by viral infections.

The literature provides information on the importance of diagnosis and treatment with the use of antiviral drugs within 72 hours, after the appearance of the rash to reduce complications. The therapy used corroborates other studies that have observed the use of antiviral in conjunction with other symptomatic drugs in Brazil and worldwide. The frequency of deaths from HZ was low, even lower than other similar studies that observed a percentage of 14.6% over five years. In Europe, mortality rates ranged from 0 to 19.5/per 100,000 inhabitants.

HZ was more frequent in the adult population and with some comorbidity associated with the condition. This makes this population the most vulnerable to reactivation of the virus and is conducive to the need for hospitalization. We can also conclude that the disease should not be underestimated due to the risk of possible complications associated with the condition. The risk factors associated with severity were the presence of vesicles and the therapy used incorrectly.

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