ORIGINAL ARTICLE

Shingles and chicken pox in the adult: markers of severity

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None

Background and objective: Diseases caused by the varicella-herpes virus in adults (chicken pox and shingles) only occasionally become serious. We sought markers that could be used in the hospital emergency department to identify adults with serious infections requiring admission.
Methods: The REVAVAZ multicenter register of adults with varicella-zoster virus infections who came to hospital emergency departments for care was used to identify variables associated with severity. Clinical and comorbidity factors underwent univariate analysis to detect attributes associated with admission in each varicella-herpes virus disease.
Results: A total of 363 cases of chicken pox and 1240 cases of Herpes Zoster were registered in 2009 and 2010; 6.9% of the adults with chicken pox and 4.2% of the adults with Herpes Zoster were admitted. Among patients with chicken pox, 71% of those under immunosuppressive treatment were admitted ($P<.01$); 38.9% of those with chest pain, 22.8% of those with cough, and and 66.7% of those with shortness of breath were admitted ($P<.01$). Among patients with Herpes Zoster, 53.8% were admitted for concomitant diseases; 82.4% of the patients with chronic obstructive pulmonary disease were hospitalized. Also admitted with Herpes Zoster were 27.2% of those with fever, 18.3% of those with chills, and 11.9% of those with muscle pain ($P<.01$). A total of 45.5% of those with neuropathy, 57.1% with respiratory disease, and 64.3% with disseminated varicella-herpes virus disease ($P<.01$) were admitted.
Conclusions: Adults with more severe chicken pox infections are those with respiratory symptoms and under immunosuppressive therapy. Patients with Herpes Zoster are admitted because of exacerbation of some concomitant disease process, especially COPD; Herpes Zoster symptoms are usually more severe in these patients. [Emergencias 2012;24:277-282]

Key words: Shingles. Adult chicken pox. REVIVAZ register.

Introduction

Chicken pox (varicella) and shingles or herpes zoster (HZ) are clinical expressions of infection by the same virus, the human herpes virus 3 or varicella-zoster virus (VZV), which belongs to the subfamily *alfaherpesvirinae,* like the *herpes simplex* virus. VZV has affinity for ectodermal cells, and is therefore dermotropic and neurotropic, which explains its pathophysiological forms[1].

Primary VZV infection is generally a mild childhood disease. However, it may sometimes be serious, especially in very young children (prenatal or perinatal chickenpox), in adults and immunosuppressed persons where it can occur in a severe form with multivisceral involvement and organ failure, typically varicella-induced pneumonia or encephalitis[2]. In Spain, seroprevalence of VZV is over 90% of the population aged > 13 years[3].

VZV remains dormant in the sensory ganglia of the spinal roots and may be reactivated with cellular immune decline, giving rise to shingles. Situations causing reactivation are diverse and more common in elderly patients (> 65 years) and in immunocompromised patients (treated with steroids or chemotherapy, infected with human immunodeficiency virus, those with bone marrow transplantation, lymphomas, neoplasia, etc.).

It is estimated that 15% of seropositive patients may have the disease and that 4-5% of these will have a second episode[3,4]. Chickenpox is a weekly notifiable disease. It is markedly seasonal with a peak in spring, in contrast to shingles with no seasonal variation, and an annual incidence of 1.3-5/1.000 population[5].

In 2005, the Public Health Commission of the National Health System Inter-Territorial Council recommended including the varicella vaccine in the childhood immunization program, to be administered to susceptible persons aged 10-14 years. After introduction, the number of varicella cases declined but there has been an increase in cases of HZ. The number of hospitalizations for HZ clearly increases with age, and 80% are patients > 50 years of age. The great majority (94%) of deaths occur in patients aged > 70 years[3].

The diseases caused by VZV, although generally mild, may present severe pictures. A better understanding of the markers of severity will therefore facilitate early identification and treatment.

The medical record is an orderly and systematic collection of certain data, observations, events or circumstances associated with a disease, syndrome or event in the field of health. Information from all cases in the form of a register constitutes the database for analysis and further study[7]. A register is not an end in itself but also serves to inform us about changes in daily clinical practice. It allows the possibility of gaining enough information to evaluate the quality of clinical practice, guide the introduction of changes and compare the results after implementation[7,8]. This feedback allows clinicians to introduce improvements in the management process (reduction of variability, morbidity and mortality)[7]. The utility of this tool is limited by problems of design, logistics, implementation, maintenance and control of the quality of the information gathered. A web-based register, with the appropriate restrictions, allows us to ensure data protection and patient confidentiality[7,9].

With the above-mentioned safeguards, the "Register of VZV infections attended by hospital emergency departments" (REVIVAZ in Spanish) was created, mainly as a source of knowledge about infectious processes and, specifically, to identify factors associated with severity in adult patients with chickenpox and HZ which determine the need for hospitalization.

Method

We used the ED-based REVIVAZ register to collect information corresponding to the periods April-August 2009 and April-July 2010 and to perform an observational, prospective, multicenter study, involving the EDs reflected in Addendum 1. "Case" was defined as an adult (> 14 years) with clinical infection by VZV attended by a participating ED during the study period. Inclusion criteria were clinically determined as follows:

– Definition of a varicella case: sudden onset with mild fever, minimal general symptoms and maculopapular type rash during a few hours with transformation into vesicles during 3 or 4 days, followed by the formation of a granular crust. The various phases coexist and lesions are superficial.

– Definition of a localized HZ case: vesicular lesions on a reddish base with a unilateral distribution limited to a dermatome. The lesions are clustered and may precede neurological symptoms such as paresthesia or pain.

– Definition of generalized HZ: lesions similar to those described above but with a distribution not limited to a particular dermatome.

Each patient was considered a case and any repeat visits for the same complaint were recorded. We recorded the following variables: demographics, clinical symptoms, risk factors, therapeutic factors and evolution. Risk factors considered were age, smoking, pregnancy, and comorbidity: kidney, liver or heart disease, hypertension, chronic obstructive lung disease - COPD, asthma, severe eczema, atopic dermatitis, spinal cord tumors, lymphomas, blood diseases, immunosuppressive therapy with corticosteroids or radiation therapy in the month before inclusion, spinal cord surgery in the previous 3 months, burns in the previous month, trauma in the previous month, diabetes mellitus, transplantation, HIV, congenital immunodeficiency and solid tumors.

The severity of the cases was estimated by the need for hospitalization. We evaluated the reason for this, distinguishing between severity of the disease itself from the existence of concurrent processes. Hospitalized patients were followed until hospital discharge or until thirty days of hospital stay.

Participating centers were issued a manual containing the inclusion criteria and definition of each variable of interest. Patient inclusion in the register required their informed consent and guaranteed data confidentiality. The project was approved by the Ethics Committee of Hospital Universitario Marqués de Valdecilla.

Results were described using estimates of central tendency for continuous variables, taking into account their distributions, and absolute and relative proportions were used for discrete variables.

Hypothesis analysis was performed to compare proportions with the chi square test with a bilateral approach. For distributions with few cases per group, we used the Fisher exact test. Continuous variables were compared using Student's t test. differences with a P value less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 15.

Results

The REVIVAZ register in 2009-2010 contributed a total of 1,603 patients: 782 in 2009 and 821 in 2010. The distribution of diseases in both periods was similar: 181 (49.9%) and 182 (50.1%) for varicella, and 601 (48.5%) and 639 (51.5%) for HZ.

During registration, 25 (6.9%) patients with varicella required admission, 24 (96%) for the disease itself. Of these patients, 16 (64%) had pneumonia. The remainder had hepatitis (3), severe varicella (3), thrombocytopenia (2) and neurological disorder (1). In patients with pneumonia, the proportion of smokers was 47% (p = 0.009 compared to those not admitted).

Of the patients with HZ, 52 (4.2%) required admission during the study. Of these, 24 (46.1%) were admitted for the disease itself, 2 for herpetic encephalitis and 28 (53.8%) for associated diseases. Of these latter patients, 8 had acute infections, 6 decompensated chronic respiratory disease, 2 constitutional syndrome, 2 previous surgery, 1 decompensated chronic renal failure, 1 heart failure, 1 cardiac arrest, 1 brain tumor, 1 decompensated diabetes and the rest had individual processes that could not be grouped.

In the group of patients with HZ, the percentage of elderly patients over 65 years admitted for concomitant pathology was 62.2% versus 37.8% for those admitted for the disease itself (p = 0.057). Previous treatment with corticosteroids was present in 81.8% of patients hospitalized for concomitant pathology, versus 12.2% of those with HZ alone (p = 0.037).

COPD as comorbidity was present in 82.4% of patients admitted for other causes and was only present in 17.6% of those admitted for HZ (p = 0.004). The other risk factors showed no difference between the two groups defined according to reason for admission.

Table 1. Risk factors and admission for herpes zoster

	Discharge	Admission	p
	N = 1188 (95.8%) N (%)	N = 52 (4.2%) N (%)	
Age > 65 years	501 (93.1)	37 (6.9)	< 0.001
Male sex	574 (94.1)	36 (5.9)	0.002
Lymphoma	15 (93.8)	1 (6.3)	0.498*
HIV	22 (91.8)	2 (8.3)	0.26*
Radiotherapy	5 (83.3)	1 (16.4)	0.22*
Renal failure	29 (87.9)	4 (12.1)	0.046*
Liver failure	26 (89.7)	3 (10.3)	0.118*
Blood Diseases	11 (73.3)	4 (36.7)	0.003*
Immunosuppression	25 (75.8)	8 (24.2)	< 0.001
Corticoid treatment	31 (73.8)	11 (25.2)	< 0.001
Diabetes	202 (95.7)	9 (4.3)	0.954
Transplantation	5 (62.5)	3 (37.5)	0.003*
Cardiopathy	135 (87.5)	19 (12.3)	< 0.001
COPD	64 (79)	17 (21)	< 0.001

COPD: Chronic obstructive pulmonary disease. *Fisher's test.

Risk factors related to severity are shown in Tables 1 and 2. The clinical symptoms associated with severity are shown in Tables 3 and 4.

In the follow-up during hospitalization, in patients with varicella there was one case of hospitalization exceeding thirty days and no deaths. However, the HZ group showed two cases of hospitalization exceeding thirty days, one death and 10 cases of organ failure of at least one organ.

Discussion

Registers of disease processes or interventions allow extending knowledge about them and the formulation of new hypotheses that may be tested. Tumor or cardiovascular disease registers have provided substantial information for improved treatment, although in our setting there are few registers developed by ED professionals. Participation in a register acts as an incentive to improve care and monitoring of clinical pathways[10].

Table 2. Risk factors and admission for varicella

	Discharge	Admission	p
	N = 338 (93.1%) N (%)	N = 25 (6.9%) N (%)	
Age > 33 years	147 (91.9)	13 (8.1)	0.27
Male sex	195 (93.3)	14 (6.7)	0.86
Pregnancy	9 (90)	1 (10)	0.51*
HIV	3 (100)	0 (0)	0.80*
Renal failure	2 (100)	0 (0)	0.86*
Asthma	11 (100)	0 (0)	0.45*
Lymphoma	1 (100)	0 (0)	0.93*
Corticoid treatment	4 (66.7)	2 (33.3)	0.058*
Immunosuppression	2 (28.6)	5 (71.4)	< 0.001*
Diabetes	8 (100)	0 (0)	0.562*
Smoking	70 (89.7)	8 (10.3)	0.185

HIV: human immunodeficiency virus. *Fisher's test.

Table 3. Clinical symptoms and admission for herpes zoster

	Discharge	Admission	P
	N = 1188 (95.8%) N (%)	N = 52 (4.2%) N (%)	
Fever	67 (72.8)	25 (27.2)	< 0.001
Pain	823 (96)	34 (4)	0.525
Chills	58 (81.7)	13 (18.3)	0.000
Vomiting	19 (95)	1 (5)	0.578*
Myalgia	89 (88.1)	12 (11.9)	0.001*
Cough	15 (78.9)	4 (21.1)	0.007*
Neurological involvement	6 (54.5)	5 (45.5)	< 0.001*
Ocular involvement	50 (4.3)	2 (5.7)	0.437
Lung involvement	3 (42.9)	4 (57.1)	< 0.001*
Disseminated herpes	5 (37.7*)	9 (64.3)	< 0.001
Superinfection	56 (88.9)	7 (11.1)	0.014*

*Fisher's test.

The data obtained in the registers have a number of limitations, mainly those relating to the selection of patients and those caused by the setting where they were collected. The REVIVAZ is an ED-based register of processes which are habitually attended in primary care and hospital settings, and provides a new perspective on VZV disease, but it is limited to this environment, where few observational studies have been performed[11].

The data obtained may be considered adequately representative since 47 hospital EDs participated, each with varying levels of care. On the other hand, the temporary nature of the register may be a limitation since it excludes cases presenting during the months of lowest incidence of varicella. This could significantly bias patient selection and mask the severity of VZV infection at other times of the year, especially in the case of HZ, where other periods may have a higher incidence and/or severity.

The percentages of adult patients with varicella and HZ were 6.9% and 4.2% respectively.

Table 4. Clinical symptoms and admission for varicella

	Discharge	Admission	p
	N = 338 (93.1%) N (%)	N = 25 (6.9%) N (%)	
Fever	211 (90.2)	23 (9.8)	0.001
Pharyngitis	74 (94.9)	4 (5.1)	0.489
Vomiting	8 (61.5)	5 (38.5)	0.001*
Myalgia	100 (93.5)	7 (6.5)	0.867
Headache	70 (92.1)	6 (7.9)	0.896
Chest pain	11 (61.1)	7 (38.9)	< 0.001*
Cough	48 (77.4)	14 (22.8)	< 0.001*
Dyspnea	5 (33.3)	10 (66.7)	< 0.001*
Hemorrhagic varicella	1 (100)	0 (0)	0.931*
Severe varicella	15 (83.3)	3 (16.7)	0.118*

*Test de Fisher.

These values are higher than those reported in primary care, which only reflects the fact that more serious cases are attended by EDs[12,13]. In the case of chicken pox the rate is unknown, but in HZ about 10% of patients are treated in the ED[14].

In patients with varicella and requiring admission, 64% had pneumonia and more serious cases had risk factors associated with decreased immune response due to immunosuppressive therapy or corticosteroids. This shows the severity that varicella may have for immunocompromised adult patients. The incidence of pneumonia in ED-treated adults with varicella was 4%, very similar to that of equivalent populations[15], but well above other rates[16], with only one case per 400 patients. The current register reveals increased severity of patients attending an ED. In the case of varicella in adults, the clinical markers of severity were respiratory signs, cough, dyspnea, chest pain and fever, consistent with the diagnosis of pneumonia which was the leading cause of hospital admission. Smoking is usually cited as a predisposing factor for the development of varicella-induced pneumonia in adults[17] and this was confirmed in the current register. However, it should be borne in mind that most of the studies citing this factor refer to patients with severe pneumonia[18].

The actual incidence of pneumonia in adults with varicella remains to be determined; figures from the literature range from the 5-50% and there are major shortcomings in the definition of varicella-induced pneumonia. Radiological anomalies are more frequent than respiratory signs, and recorded in 16% of young people with varicella[19]. The presence of vomiting, although very nonspecific, is described as a clinical symptom of varicella in adults[19]. The low mortality of the patients in the present study, including those with pneumonia, seems to contrast with reference rates in the literature, but mortality has progressively declined in recent years[19].

Although usually considered a benign disease, HZ is not free of potential complications[20]. Patients with HZ are admitted to hospital for concurrent processes, mostly infection or chronic disease decompensation. The presence of neurological involvement is a criterion of severity. The use of hospital admission registers only to assess the burden of HZ in hospitalization in our country has important limitations[21]. The most important aspect is that only 4.2% of patients with HZ required admission and, of these, only 42.3% were admitted for HZ itself, while the remainder were admitted for concomitant processes. Pa-

tients with COPD showed the greatest susceptibility, as previously described[22].

The severity of HZ is greater in patients on immunosuppressive treatment and those with comorbidities likely to decompensate such as renal, cardiac or respiratory disease. Hospital admission is more frequent in males than females, patients over 65 years, and those admitted for conditions associated with elderly age[21,22].

From the present work we can conclude that the ED-based register of VZ diseases provided us with a better understanding of varicella and HZ in adults. Severity estimated by the percentage of admission was higher than that reported in the literature for adults with varicella or HZ. Factors that increase severity in adults with varicella are the presence of immunosuppression, respiratory symptoms, fever and vomiting. In addition, hospital admission of patients with HZ is associated with older age, male sex, chronic conditions such as heart disease, renal failure and COPD, and diseases with immunosuppression including transplant patients and those with hematologic disease. Patients presenting with fever, respiratory or neurological disorders and those with disseminated HZ also showed greater severity.

Annex

The following hospital (H) centers participated in the present study: H. San Jaime de Torrevieja, H. Comarcal de Elda, H. Comarcal de Baza, H. Clínico San Cecilio de Granada, H. Comarcal de Monforte de Lemos, H. Carmen y Severo Ochoa de Cangas de Narcea, H. Do Meixoeiro de Vigo, H. Dr. Rafael Méndez de Lorca, H. General Reina Sofía de Murcia, H. Puerta del Mar de Cádiz, H. Universitario de Puerto Real, H. de Montilla, H. Ntra. Sra. de la Merced, H. Reina Sofía de Córdoba, H. Royo Villanova de Zaragoza, H. Espirit Sant de Barcelona, H. San Camilo, H. Igualada de Barcelona, H. Santa Tecla de Tarragona, H. Arnau de Vilanova, H. Mataró, H. Univ. Mutua de Terrassa, H. Río Hortega de Valladolid, H. Clínico Valladolid, H. Barbanza de Oleiros, H. Virgen del Puerto de Plasencia, H. Virgen de la Salud de Toledo, H. Virgen de la Luz de Cuenca, H. San Eloy de Barakaldo, H. Zumárraga, H. Bidasoa, H. General Universitario, H. La Ribera de Alzira, H. La Plana de Villarreal, H. Sagunto, Clínica Juaneda de Palma de Mallorca, H. Costa del Sol de Marbella, H. Sierrallana de Torrelavega, H. Jové de Gijón, H. Univ. Canarias, H. Móstoles, H. 12 de Octubre de Madrid, H. Puerta de Hierro de Majadahonda, H. Clínico San Carlos de Madrid, H. Príncipe de Asturias de Alcalá de Henares, H. La Moraleja, H. Univ. Marqués de Valdecilla de Santander.

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Marcadores de gravedad en el herpes zóster y la varicela del adulto

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Objetivo: Las enfermedades generadas por el virus varicela zóster en el adulto, varicela y herpes zóster (HZ), sólo ocasionalmente tienen un curso grave. Se plantea la identificación de marcadores de gravedad en los pacientes adultos atendidos en los servicios de urgencias hospitalarios a través de la necesidad de ingreso hospitatalario.
Método: El registro multicéntrico de pacientes adultos con infecciones por virus varicela zóster atendidos en servicios de urgencias (REVIVAZ) se usó para la identificación de factores asociados a gravedad. Mediante un análisis univariable se identificaron los factores de comorbilidad y clínicos que se asociaron al ingreso en cada una de las dos formas de la enfermedad.
Resultados: Durante los años 2009 y 2010 se han registrado 363 casos de varicela y 1.240 de HZ. El porcentaje de pacientes adultos ingresados con varicela fue el 6,9% y con HZ el 4,2%. Los casos de varicela que tenían tratamiento inmunosupresor ingresaron en el 71% ($p < 0,01$ respecto al resto), los que presentaban clínica de dolor torácico, tos y disnea fueron ingresados en el 38,9%, 22,8% y 66,7% respectivamente ($p < 0,01$ respecto al resto para cada uno de ellos). Los casos de HZ ingresados lo fueron en el 53,8% por patologías asociadas y la enfermedad pulmonar obstructiva crónica (EPOC) estuvo presente en el 82,4% de los pacientes. Los casos de HZ con fiebre, escalofríos y mialgias ingresaron en el 27,2%, 18,3%, y 11,9%, respectivamente ($p < 0,01$ respecto del resto para cada uno de ellos). El porcentaje de ingreso con una afectación neurológica fue del 45,5%, con afectación pulmonar del 57,1% y con herpes diseminado del 64,3% ($p < 0,01$ respecto al resto para cada uno de ellos).
Conclusiones: Los pacientes con varicela de mayor gravedad acuden con clínica respiratoria, y el tratamiento inmunosupresor se asocia a mayor gravedad. Los pacientes con HZ ingresan por descompensación de otro proceso, fundamentalmente de EPOC, y la clínica de infección en el paciente con HZ se asocia a una mayor gravedad. [Emergencias 2012;24:277-282]

Palabras clave: Herpes zóster. Varicela del adulto. REVIVAZ.