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Demography, Symptomatology, and Course of Disease in Ambulatory Zoster Patients

A Physician-Based Survey in Germany[1]

Summary

This survey summarises the observations of physicians who prospectively recorded clinically relevant data on their patients with an episode of herpes zoster. These included demography of patients, signs and symptoms during the prodromal phase, relevant history, description of disease at the first visit, therapeutic measures and description of disease, and occurrence of postherpetic neuralgia (pain 4–5 weeks after crusting) at the second visit. A total of 2,063 patients were reported to the data management centre. The age distribution resembles that reported in the literature including the notable increase in zoster frequency with advancing age. Almost 20% of the patients, however, were 30 years old or less, and this contrasts markedly with the published literature. Age modifies the frequency of the dermatome afflicted: more cranial and less thoracic manifestations were observed with increasing age. Almost all patients reported symptoms which may be attributed to a prodromal phase, especially pain in the affected dermatome (82%). The incidence of postherpetic neuralgia was 28%. A complicated disease course such as visceral, ocular, or otological involvement, or progression to additional dermatomes was seen in almost 10% of the patients.

Key Words

Herpes zoster
Epidemiology
Symptomatology
Demography
Prodromal phase
Complications
Survey

Introduction

Zoster can appear in many disguises, especially in the pre-eruptive phase. Patients may present with their complaints to either dermatologists, specialists for internal medicine, or commonly to their family doctors. Although some aspects of the intriguing pathophysiology – reactivation of a latent, neuronal varicella zoster infection – have been clarified [1, 2], other aspects particularly of the most important complication, postherpetic neuralgia, still need clarification [3–5].

Our current knowledge of the epidemiology of zoster is based mostly on data collected 30–40 years ago. Furthermore, most of these studies are either large case series by a single observer [6, 7] or are hospital-based studies [8]. A large population-based study covers the period 1945–

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1959, but this is a retrospective study and lacks details on some practical clinical aspects [9]. After completion of this study, a population-based investigation of incident and recurrent zoster in a health maintenance organisation reported a 64% higher incidence of herpes zoster (215 cases per 100,000 person-years) than that reported 30 years previously [10], raising the question as to whether characteristics of the disease may have changed as well. The availability of new orally administered antiviral drugs such as famciclovir, valaciclovir, and brivudin with the potential to reduce the incidence of sequelae if given early, stimulated the interest in current epidemiological data with clinical relevance [11–16].

The objective of this survey was to summarise the observations of a sizeable group of physicians who prospectively recorded clinically relevant data including the demography of patients, signs and symptoms during the prodromal phase, relevant history, description of disease as observed at the first visit, therapeutic measures, description of disease at follow-up visit, and occurrence of postherpetic neuralgia. In addition, the question of secular trends of patients presenting to the physician is addressed in comparison with earlier publications.

The risk factors for the development of the most relevant complication, postherpetic neuralgia in patients who did not receive antiviral therapy, have been described in a separate publication [17].

Methods

General Study Plan

Physicians were selected randomly from the German physicians inventory with two aims: a distribution across the whole of Germany and a split between the specialities that represents the actual distribution of presentation of zoster patients to physicians (50% family physicians, 33% dermatologists and 17% specialists in internal medicine, according to market research estimates). Each doctor was mailed a short announcement with a reply card. Interested physicians were sent a description of the study and case record forms.

The protocol asked the physicians to document prospectively all cases of zoster during the study. There were no recommendations or exclusion criteria concerning systemic antiviral, other systemic (analgesic) or topical therapy.

The data from each case were collected at three time points: the first visit, the second visit when cutaneous lesions had fully crusted, and 4–5 weeks after full crusting for assessment of postherpetic neuralgia.

The physicians were asked to send each case record form after completion to the data management centre (gmi; Gesellschaft für Angewandte Mathematik und Informatik, Munich). There, data were entered by double data entry into a relational data base; if the internal computerised plausibility check flagged a problem, queries were sent to the physician and the case was only included after a satisfactory response was obtained. For the purpose of this publication, the analysis of the data was descriptive.

Collected Data

At the first visit, the following data were collected: sex, age, relevant history (e.g. malignant disease, allergy, immunosuppressive therapy), presence and duration of prodromal signs and symptoms (e.g. elevated body temperature, dermatomal pain, malaise, unspecific flu-like pain), descriptive data of disease [localisation, characteristics of the cutaneous lesions (extent of skin covered, number and description of the lesions), intensity of acute zoster pain, and others], intended therapy (systemic antiviral therapy, other systemic therapy including pain therapy, topical therapy, non-drug pain therapy). A second visit was scheduled at the time of crusting of skin lesions in order to reassess the signs and symptoms (number of lesions, time point of crusting, zoster-related pain, complications). Finally, the occurrence of postherpetic neuralgia was ascertained 4–5 weeks after crusting.

Results

Study Population

The patients were recruited from September 1994, until March 1995. A total of 4,542 physicians were initially contacted. Other physicians asked to participate and were accepted. 582 physicians requested the study documentation and 486 contributed patients. 48% of the physicians were dermatologists, 44% family physicians, and 8% specialists for internal medicine. A total of 2,063 patients were reported to the data management centre (64% by dermatologists, 31% by family physicians, 5% by specialists for internal medicine).

Demographic Data

55.4% of the patients were females and 44.6% were males. The age distribution, stratified for sex and compared with the age distribution of the German population, is shown in figure 1. The curve resembles that reported in the literature, including the notable increase with age [7, 9]. Nevertheless, the contribution of younger age groups is surprisingly high with almost 20% of the patients being younger than 30 years of age. The difference in the proportion of males and females in each age group in this study appears to reflect the difference in the male to female ratio in the general German population (fig. 1).

Pre-existing conditions were reported with the following frequencies: malignancies 5.1%, insulin-dependent diabetes mellitus 5.0%, allergy 12.4%, atopic dermatitis 5.5%, radio-/chemotherapy 1.5%, other immunosuppressive therapy 2.7%. 64% of the cases were reported without any known pre-existing condition.

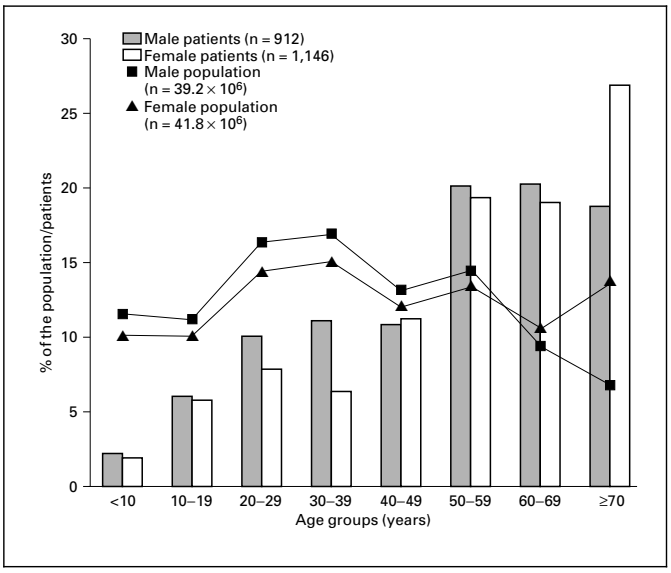

Fig. 1. Age and sex distribution among patients with herpes zoster compared with the data from the German general population in 1993.

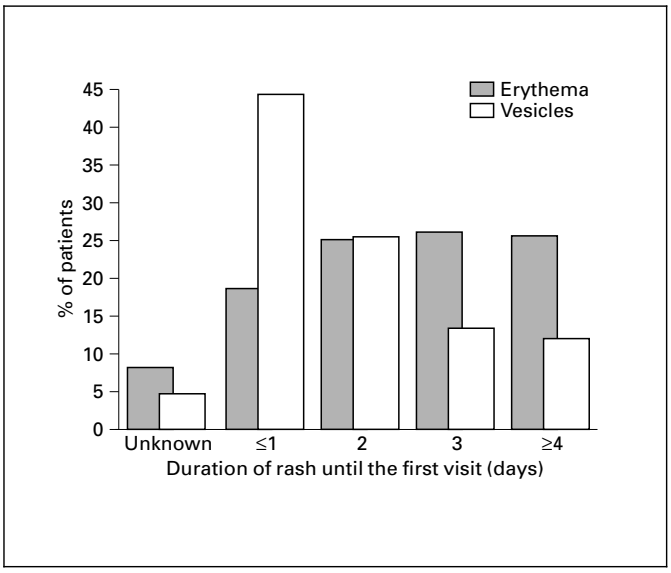

Fig. 2. Reported duration of zoster rash at presentation to the physician.

Table 1. Complicated courses of herpes zoster (except postherpetic neuralgia) (n = 2,063)

Complication	Number of cases		
	1st visit	2nd visit	total cases
Visceral involvement	11	5	16
Zoster ophthalmicus	44	11	55
Zoster oticus	12	6	18
Segmental paresis	35	6	41
Extension to further dermatomes	n.a.	24	24
Other (not specified)	0	31	31
Total	102	83	185

n.a. = Not applicable.

Prodromal Phase

Almost all patients reported symptoms which may be attributed to a prodromal phase before the diagnosis of zoster was made. The leading symptom was pain/burning in the afflicted dermatome (81.6% of patients); unspecific flu-like headache or limb pain were reported for 38.9% of the cases. Paresthesias were reported by 33% of the patients. Other symptoms included: malaise (44.9%), nocturnal sweating (19.2%), elevated body temperature (13.6%) and nausea (10.6%).

Manifestations of Disease

A unilateral cutaneous rash usually confined to one dermatome is the salient feature of zoster. The reported duration of the rash at presentation to the physician is summarised in figure 2. At least one quarter of the patients had consulted a physician for the first time only 3 days or more after onset of a vesicular rash.

In 66% of patients only one dermatome was affected, in 31.2% two adjacent dermatomes, and 2.8% had either dissemination, or more extensive or distant cutaneous manifestations of zoster. The most frequent localisation was thoracic, and the least frequent was sacral (fig. 3). Due to the methodological differences (e.g. population-based versus physician-based) between this study and previously studies also shown in figure 3, the comparison may not be statistically correct; nevertheless, on visual inspection, the results appear to be in general agreement [7, 9].

Age modifies the frequency of the dermatome afflicted. With increasing age, more cranial and less thoracic manifestations were observed, but the other localisations remained constant (fig. 4).

The lesions were described as hemorrhagic in 16.2% of cases. In the majority of patients, the number of lesions was below 25 (53.7%). In 32.8% of patients, there were between 25 and 50 lesions, in 10.8% between 51 and 100, and in 2.7% more than 100 lesions. At the first visit, the

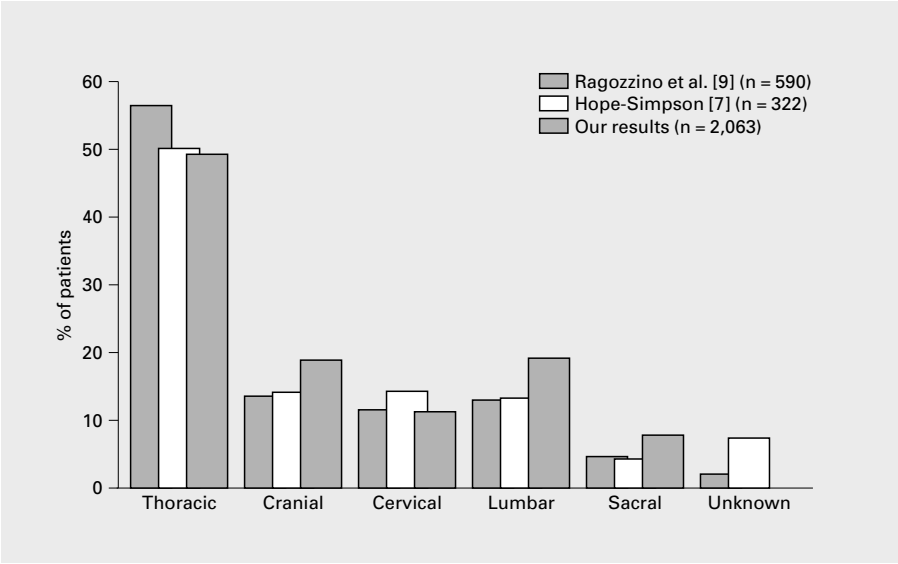

Fig. 3. Dermatomal localisation of herpes zoster in comparison with the studies by Ragozzino et al. [9] and Hope-Simpson [7].

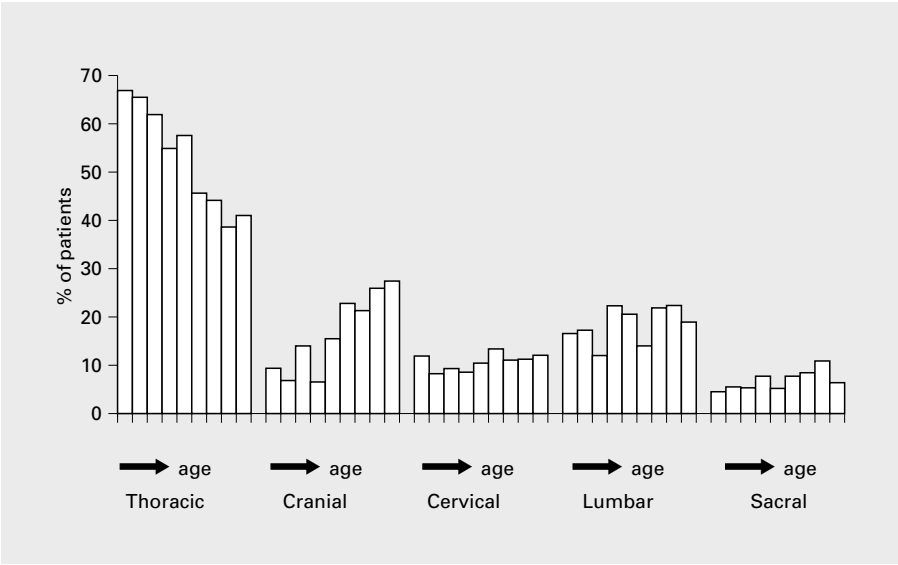

Fig. 4. Age dependency of zoster localisation. 1st segment: <10 years; 2nd segment: 10–19 years; 3rd segment: 20–29 years; 4th segment: 30–39 years; 5th segment: 40–49 years; 6th segment: 50–59 years; 7th segment: 60–69 years; 8th segment: 80–90 years. The thoracic localization decreases, the cranial localization increases with age.

following complications were noted: visceral (e.g. pulmonary) involvement 0.5%, otologic involvement 0.6%, and segmental paresis 1.7%. At the second visit, crusting had completed in 85.8% of patients; but in 1.2% of patients, the cutaneous lesion had spread to a new dermatome. Additional complications/special courses are summarised in table 1. 68% of the patients received antiviral therapy (at the time of this survey, only aciclovir was marketed for the treatment of zoster).

Zoster-Related Pain

Almost all patients suffered from pain in the afflicted area. The frequency of this dominant symptom at different time points during the study and according to different intensities is summarised in figure 5. In the prodromal phase, the patients were asked whether they had experienced 'pain or a burning sensation' in the area of the rash prior to its appearance. At the subsequent time points, patients were asked to classify their pain in the afflicted area as severe ('unbearable' in spite of pain medication), moderate ('pain medication successful') or light ('no need for pain medication').

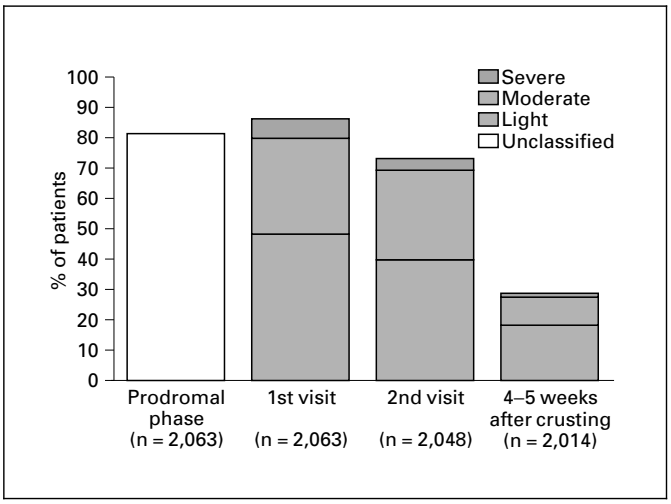

Fig. 5. Intensity of zoster-associated pain at different time points. Pain severity was classified as light (tolerable without pain medication), moderate (tolerable with pain medication), severe (severe despite pain medication). Pain during the prodromal phase was not classified.

The data show the following: firstly, that the proportion of patients who experienced pain prior to the first visit is similar to that reporting pain at the first visit. Of course, patients with a cutaneous lesion without pain may decide not to see a physician. Secondly, pain refractory to analgesic therapy is reported by a sizeable 7.5% of the patients. Thirdly, the incidence of postherpetic neuralgia defined as pain in the afflicted dermatome 4–5 weeks after crusting is high (28.4%).

Discussion

A review of the literature shows a considerable lack of recent data about the signs and symptoms of zoster; in fact, the most frequently quoted paper is based on observations from the post-war era [7]. A more recent paper using a population-based approach reported a marked increase in zoster [10].

Therefore, a physician-based survey was designed attempting to collect the data of all new zoster patients presenting to the participating physicians in Germany. This approach describes the features of the patients as they present themselves to the physicians; it does not give information concerning the incidence or prevalence of zoster in either the total population or a subgroup (e.g. age groups), or prognostic factors for the occurrence of zoster. In this respect, population-based approaches have shown that non-detected malignancies or diabetes mellitus did not increase the risk of zoster; in the elderly, zoster is much less common in the black as compared to the Caucasian population [18–20].

Like other studies, this study suggests a higher incidence in females. Two independent population-based surveys, however, did not confirm sex as a risk for the occurrence of zoster after correcting for the sex differences in the elderly population [7, 20]. A third study found a similar incidence [9]. This difference can be explained by the combination of increased incidence in the older age group with the preponderance of women in this age group (fig. 1).

The association of age with the occurrence of zoster agrees with existing data, showing a pronounced increase in older age groups (fig. 1) [7, 9, 10]. Nonetheless, a perception of zoster being a disease of the elderly is wrong: 25.3% of the ambulatory patients were under the age of 40 years, 6% under the age of 20 years and 2% even under the age of 10 years. This observation agrees well with the reported incidence of 5% for children under the age of 15 years [10].

A major objective of this survey was to record signs and symptoms of zoster in the prodromal phase. The outstanding finding was certainly the presence of a dermatomal pain or burning sensation in 81.7% of patients. This was accompanied by non-specific symptoms such as elevated body temperature, nocturnal sweating, non-specific pain, malaise or nausea. This suggests the possibility of diagnosing zoster before the development of the classical picture, although the data cannot give information concerning the sensitivity and specificity of these symptoms.

Interestingly, 22.8% of the patients consulted a physician during the prodromal phase and in 39.2% of those the correct diagnosis of zoster was suspected prompting an antiviral therapy in 73 patients (15.9% of those visiting a physician during the prodromal phase). Pathophysiological considerations and clinical data call for early antiviral therapies [21]. 25.6% of the patients consulted a physician after the time window for starting successful therapy had already passed [21].

The localisation of the zoster was in accordance with existing data (fig. 3) [7, 9]. A complicated course such as visceral (e.g. pulmonary), ocular, or otological involvement, or progression to additional dermatomes, was seen in almost 10% of the patients, a number much higher than expected. Remarkable results were the frequent involvement of the trigeminal area and the development of a typical zoster oticus. Whether these numbers reflect a secular

trend or are an artefact resulting from a high number of dermatologists participating in the survey remains to be resolved.

The high number of patients enabled us to look at age trends in localisation; there are no comparable literature reports. Clearly, the thoracic localisation becomes less frequent and the cranial one more frequent with increasing age with the three other localisations remaining apparently unchanged (fig. 4).

This finding is in agreement with the increasing risk of postherpetic neuralgia with age and the higher risk of postherpetic neuralgia with the cervical localisation. We are unable to formulate a plausible hypothesis for this observation.

The main complaint, second to the cutaneous lesions, is zoster-related pain (fig. 5). An unexpected high incidence of pain was reported for the prodromal phase. Pain refractory to analgesic therapy is reported by a group of patients (7.5% at the first visit, 4% at the second visit), and this underlines the enormous impact of this disease on the quality of life of patients. The incidence of postherpetic neuralgia was 28.4% in the reported range [1, 5]. A detailed analysis of postherpetic neuralgia, including an attempt to predict its development based on data available at diagnosis, is the subject of a separate publication [17].

In conclusion, this physician-based survey confirmed existing data on age and sex distribution of patients presenting with herpes zoster, but also yielded new information, notably the decrease in thoracic and the increase in cervical localisation with advancing age. The proportion of younger patients, although lower than that of elderly patients, was yet sizeable in these ambulatory patients. A prodromal phase was the rule. The rate of complications was high. Further efforts are warranted to describe zoster in the younger population and in complicated cases, to define risk factors for the development of postherpetic neuralgia, to enhance the capability to diagnose zoster earlier, and to educate patients to visit their doctor earlier.

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