Clinical Diagnosis of Herpes Zoster in Family Practice

Wim Opstelten, MD, PhD[1]
Anton M. van Loon, PhD[2]
Margje Schuller, MSc[2]
Albert J. M. van Wijck, MD, PhD[3]
Gerrit A. van Essen, MD, PhD[1]
Karel G. M. Moons, PhD[1]
Theo J. M. Verheij, MD, PhD[1]

[1]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, The Netherlands

[2]Department of Virology, Eijkman-Winkler Center, University Medical Center Utrecht, The Netherlands

[3]Department of Anesthesiology, University Medical Center Utrecht, The Netherlands

ABSTRACT

PURPOSE Family physicians usually diagnose herpes zoster on clinical grounds only, possibly resulting in false-positive diagnoses and unnecessary treatment. We wanted to determine the positive predictive value of the physicians' judgment in diagnosing herpes zoster and to assess the applicability of dried blood spot analysis for diagnosis of herpes zoster in family practice.

METHODS Our study population consisted of 272 patients older than 50 years with herpes zoster (rash for less than 7 days). Dried blood spot samples were collected from all patients and sent by mail to the laboratory. Baseline measurements included clinical signs (localization, severity, and duration of rash) and symptoms (duration and severity of pain). Varicella-zoster virus antibodies were determined at baseline and 5 to 10 days later. Multivariate logistic regression was used to assess independent associations between clinical variables and serological confirmation of herpes zoster.

RESULTS Dried blood spot analysis was possible in 260 patients (96%). In 236 the diagnosis of herpes zoster was confirmed serologically (positive predictive value of clinical judgment 90.8%; 95% confidence interval, 87.3%-94.3%). Independent clinical variables for serologically confirmed herpes zoster were severity and duration of rash at first examination.

CONCLUSION Family physicians have good clinical judgment when diagnosing herpes zoster in older patients. Dried blood spot analysis is a logistically convenient method for serological investigation of patients in family practice, but it is rarely needed for diagnosing herpes zoster.

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INTRODUCTION

Herpes zoster is a common disease, with a reported incidence varying from 2.2 to 4.8 per 1,000 persons per year.[1-3] It is due to a localized recrudescence of the varicella-zoster virus in sensory ganglia, where the virus has remained dormant since the primary infection (chickenpox). Age and immunity-attenuating diseases are well-known risk factors for herpes zoster.[4] The most frequent complications of herpes zoster include postherpetic neuralgia and, in cases of ophthalmic herpes zoster, sight-threatening eye problems.

Because the typical unilateral rash helps family physicians diagnose herpes zoster clinically, suspected cases of herpes zoster are rarely investigated serologically or virologically. False-positive diagnosis of herpes zoster, however, is reported to occur in up to 13% of patients[5,6] and may result in unnecessary prescription of antiviral medications, erroneous referral, and unnecessary invasive interventions for the prevention of postherpetic neuralgia.[7]

Serological analysis is one method to confirm the diagnosis of herpes zoster,[8] but few studies have assessed its value in family practice. Moreover, such analysis in primary care can be fraught with logistic problems. In remote areas laboratory facilities may not be accessed easily, and for research purposes uniform analysis techniques at a central location may

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CORRESPONDING AUTHOR

Wim Opstelten, MD, PhD
Julius Center for Health Sciences and Primary Care
University Medical Center Utrecht
PO Box 85060
3500 AB Utrecht, The Netherlands
w.opstelten@umcutrecht.nl

be preferred over analyses in different laboratories. To address these problems in resource-limited settings, dried blood spot analysis has been used for the screening and diagnosis of various infectious diseases, including those caused by varicella-zoster virus,[9] as it greatly facilitates collection and transport of patient material and assures its stability.[10,11]

The aims of this study were to determine the positive predictive value of clinical judgment in diagnosing herpes zoster and to assess the logistic appropriateness of dried blood spot analysis in primary care.

METHODS

Patients and Setting

The study population consisted of 272 patients who had been consecutively included as a subgroup in the Prevention by Injection of Postherpetic Neuralgia in the Elderly (PINE) study.[12,13] From September 2001 to February 2004, family physicians in different regions of the Netherlands included patients older than 50 years who had acute herpes zoster (rash for less than 7 days) below dermatome C6 and who were immunocompetent but had no known serious disorder of the immune system (eg, acquired immunodeficiency syndrome). Physicians examined their patients during normal practice hours and based their diagnosis of herpes zoster on their clinical judgment. Because the family physicians participating in the study were scattered over the country, dried blood spot serological analysis was considered a suitable method for patients' blood investigation. To assess possible selection, during the study the participating family physicians registered the baseline characteristics of herpes-zoster patients who were both included and not included in the study.

Baseline measurements included severity (visual analogue scale ranging from "no pain" at 0 mm to "worst pain ever experienced" at 100 mm[14]) and duration of pain before the enrollment visit. Also included were onset, severity (0 to 20 vesicles, mild; 21 to 46 vesicles, moderate; 47 and more vesicles, severe),[15] and localization (cervical, thoracic, lumbar, and sacral) of the rash.

In most cases, collection of finger-prick blood was performed by the physicians' assistants in the same manner as regular fasting blood glucose checks in diabetic patients.

The medical ethics committee of the University Medical Center Utrecht approved the study protocol.

Clinical Specimens

Finger-prick blood from each patient was collected on at least 3 of 6 circles (13 mm in diameter) printed on filter paper at the time of inclusion (sample 1) and between 5 and 10 days later (sample 2). After drying at room temperature, the dried blood spot samples were transferred to plastic bags and sent from the family practices to the Department of Virology at the University Medical Center Utrecht, where they were stored at 4°C for up to 18 months before testing. Immunoglobulin M, A, and G antibodies to varicella-zoster virus (VZV-IgM, VZV-IgA and VZV-IgG) or herpes simplex virus (HSV-IgM, HSV-IgA and HSV-IgG) were determined using a commercial enzyme-immunoassay (Enzygnost, Dade Behring, Marburg, Germany).

Preliminary research in 4 healthy volunteers showed that preservation of the blood samples up to 8 days after collection at room temperature and at 37°C did not measurably affect the titers of VZV-IgG antibodies. In view of earlier research[10,11,16] and our own 8-day experience with accelerated stability testing at 37°C, we felt confident that storage for 18 months at 4°C would not affect our results.

Serological analysis on herpes simplex virus was performed in all patients in whom varicella-zoster virus could not be confirmed serologically.

To avoid biased selection of patients, the participating family physicians were not informed about the diagnostic purpose of the blood samples.

Data Analysis

We first estimated the frequency in which the family physicians' clinical diagnosis was confirmed by serological analysis. Patients were considered to have serological evidence of herpes zoster if 1 or both dried blood spot samples were positive for IgM antibodies or IgA antibodies, and/or if they had a greater than 2.5-fold rise in IgG antibodies in paired samples. Because we did not include patients for whom the family physicians rejected the herpes-zoster diagnosis, we could only assess the positive predictive value of the clinical judgment, not the negative predictive value, sensitivity, or specificity. We then quantified whether those patients with and without serologically confirmed herpes zoster differed in their clinical signs and symptoms using multivariate logistic regression analysis. To make the analyses more statistically sound, we collapsed severity and localization variables across the levels. We additionally assessed the associations between the increased levels of the 3 varicella-zoster virus antibodies and the administered interventions (antiviral therapy and epidural injection of steroids plus local anesthetics) using multivariate linear regression analysis. All data were analyzed using SPSS for Windows, version 12.0 (SPSS Inc, Chicago, Ill).

RESULTS

Paired blood samples of 272 consecutive herpes-zoster patients were received at the laboratory. The median

time span between collection of the blood and delivery at the laboratory amounted 4 days (interquartile range: 2 to 6 days). In 12 patients 1 or both samples did not contain sufficient blood for serological analysis. In the remaining 260 patients that were used in the further analyses, at least 6 serological analyses could be performed from each collected blood sample. The median duration of the zoster rash at the enrollment visit was 2 days (interquartile range: 1 to 4 days). The median time between the 2 blood specimens was 7 days (10%-90% range: 7 to 9 days).

Serologic Testing and the Clinical Diagnosis of Herpes Zoster

The clinical diagnosis herpes zoster was confirmed serologically in 236 patients (positive predictive value = 90.8%; 95% CI, 87.3%- 94.3%). The diagnosis was established by the presence of VZV-IgM antibodies in 81 (34.3%) patients, by the presence of VZV-IgA antibodies in 221 (93.6%) patients, or by a greater than 2.5-fold rise in VZV-IgG antibodies in 148 (62.7%) patients. In 144 (61.0%) patients, analysis of the first blood sample confirmed the diagnosis. The first blood sample was positive for VZV-IgM antibodies in 40 (16.9%) patients and was positive for VZV-IgA antibodies in 134 (56.8%) patients.

Demographic and clinical characteristics of patients with and without serologically confirmed herpes zoster are displayed in Table 1. The only independent clinical variables for serologically confirmed herpes zoster were severity and duration of rash at examination. There was no multicollinearity between the studied predictor variables.

Rises in varicella-zoster virus antibodies or a lack thereof were not associated with antiviral treatment or with epidural administration of steroids (data not shown).

Alternative Diagnoses

With regard to the 24 unconfirmed cases, 1 patient (male, aged 60 years) had a 2.5-fold increase in HSV-IgG, indicating a recent herpes simplex virus infection. HSV-IgA antibodies were not present in any of the patients without serological confirmation of herpes zoster. On clinical reevaluation, another patient (female, aged 52 years) had a bacterial skin infection, and a third (female, aged 68 years) an immune deficiency disorder. The clinical course in the remaining 21 patients did not cause family physicians to revise their initial diagnosis of herpes zoster. Among these 21 patients, 2 appeared to be (VZV-IgG) seronegative (1 woman aged 58 years, and 1 man aged 67 years).

DISCUSSION

In this study of herpes zoster in primary care, we found that the clinical diagnosis could be confirmed serologically in 91% of patients with signs and symptoms of herpes zoster. This study therefore shows that family physicians have good clinical judgment with regard to diagnosing herpes zoster, a finding all the more impressive when considering that the percentage of unconfirmed cases could have been lower had an even more sensitive test (ie, polymerase chain reaction for VZV-DNA from vesicle fluid[17,18]) been used to confirm the clinical diagnosis.

Table 1. Demographic and Clinical Characteristics of Herpes-Zoster Patients With and Without Serological Confirmation (n = 260)

Characteristic	With Confirmed HZ (n = 236)	Without Confirmed HZ (n = 24)	Univariable OR (95% CI)	Multivariable OR (95% CI)
Age, mean (SD), y	66.5 (9.7)	63.9 (9.9)	1.03 (0.98-1.08)	1.05 (0.99-1.10)
Female sex, No. (%)	133 (56.4)	13 (54.2)	1.09 (0.47-2.54)	0.88 (0.32-2.39)
Duration of rash at examination, mean (SD), d	2.7 (1.7)	1.9 (1.9)	1.39 (1.04-1.85)	1.60 (1.13-2.29)
Severity of rash at examination*				
Mild,† No. (%)	88 (37.3)	19 (79.2)	–	–
Moderate/severe, No. (%)	144 (61.0)	5 (20.8)	6.22 (2.24-17.25)	5.21 (1.75-15.54)
Localization				
Other,† No. (%)	59 (25.0)	8 (33.3)	–	–
Thoracic, No. (%)	177 (75.0)	16 (66.7)	1.50 (0.61-3.68)	2.14 (0.73-6.29)
Duration of prodromal pain, mean (SD), d	2.4 (3.9)	2.5 (2.7)	0.99 (0.89-1.11)	1.04 (0.88-1.22)
Severity of pain,‡ mean (SD)	48.3 (26.9)	46.9 (28.0)	1.00 (0.99-1.02)	0.99 (0.98-1.02)

HZ = herpes zoster; OR = odds ratio; CI = confidence interval.

* Dermatome was unknown in 4 patients with serological confirmation of herpes zoster.

† Reference category.

‡ Visual analog scale, range 0-100.

The diagnosis could not be confirmed serologically in 9% of the patients with clinically diagnosed herpes zoster. This percentage is comparable to results reported by Kalman and Laskin[5] and Helgason et al.[6] Our study, however, is the first in which consecutive primary care patients with clinically diagnosed herpes zoster were serologically investigated prospectively, whereas Kalman and Laskin performed viral culture only in a small group of referred herpes-zoster patients (47 patients), and Helgason et al verified the clinical diagnosis of herpes zoster mainly by reviewing the clinical characteristics of patients. In contrast with the Helgason et al study, we found recent herpes simplex virus reactivation in only 1 patient. This finding can be explained by the higher mean age of our study population; in contrast with herpes zoster, the incidence of herpes simplex virus recurrence has been reported to decrease with age.[19]

The only independent clinical variables for serologically confirmed herpes zoster were severity and duration of rash at the enrollment visit. Although zoster without rash has been reported (so-called zoster sine herpete),[20] the typical appearance of vesicles is a highly distinguishing sign for herpes zoster.

VZV-IgA assay contributed most to the confirmation of the clinical diagnosis of herpes zoster. Because only 57% were positive for VZV-IgA during the first days of the zoster rash, this test is not suitable for identifying acute herpes zoster, ie, at a time when confirmation of the diagnosis may have prompt therapeutical consequences. Combination with a VZV-IgM assay would hardly improve detection (Table 1). A polymerase chain reaction on VZV-DNA from vesicle fluid would be preferred in such a situation.[17,18,21]

Of the 272 blood samples, 260 (96%) were suitable for serological analysis, so this diagnostic method proved logistically feasible in primary care, as has previously been described for a variety of infectious diseases, including measles, toxoplasmosis, hepatitis C, and human immunodeficiency virus infection.[16,22-24] Although our study shows that the value of dried blood spot for serological verification of herpes zoster is limited, the logistic advantages of this method, such as ease of collection, transport, and storage, are evident.

Some potential limitations of this study need to be addressed to appreciate the results. First, our aim was to quantify the extent to which a clinical diagnosis of herpes zoster made by the family physician could be confirmed serologically. As a result, we studied only those patients with herpes zoster diagnosed clinically by their physician. We did not aim to determine the value of serologic testing as reference standard for all patients suspected of having herpes zoster. Hence, we could quantify only the positive predictive value of the family physician's clinical diagnosis, which was 90.8%; we could not assess the corresponding sensitivity, specificity, negative predictive value, and likelihood ratios. Second, because of the inclusion criteria of the randomized clinical trial in which this study was nested, the results apply only to older (older than 50 years) immunocompetent patients with herpes zoster below the C6 dermatome. Because immunosuppression may cause deficient antibody production,[25] VZV-serological tests might perform less well in immunocompromised patients. Such patients, however, are at high risk of complications from viral dissemination, and any clinical diagnostic uncertainty should justify prompt referral for specialized care and laboratory investigation. There is no evidence that herpes-zoster patients younger than 50 years or those with cranial (eg, ophthalmic) localization have a diminished serological response to a VZV-reactivation. Finally, patient selection with typical signs and symptoms could have occurred had only patients with typical signs and symptoms of herpes zoster been enrolled in the PINE trial from which this study was derived. The participating family physicians, however, registered the baseline characteristics of all new herpes-zoster patients who visited them during the inclusion period. These data did not differ between enrolled patients and patients who met the inclusion criteria but were not enrolled. We therefore consider the results of this study to be valid for all immunocompetent herpes-zoster patients in family practice.

We conclude that the clinical diagnosis of herpes zoster made by family physicians is correct in more than 90% of cases in which serologic testing was used as a reference standard. Thus, VZV-antibody analysis does not have added value as a routine diagnostic aid in family practice. Our results, however, show that dried blood spot analysis is a logistically convenient method for serological investigation of patients in primary care.

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References

1. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. *Arch Intern Med.* 1995;155(15):1605-1609.
2. Galil K, Choo PW, Donahue JG, Platt R. The sequelae of herpes zoster. *Arch Intern Med.* 1997;157(11):1209-1213.

3. Chidiac C, Bruxelle J, Daures JP, et al. Characteristics of patients with herpes zoster on presentation to practitioners in France. *Clin Infect Dis.* 2001;33(1):62-69.

4. Thomas SL, Hall AJ. What does epidemiology tell us about risk factors for herpes zoster? *Lancet Infect Dis.* 2004;4(1):26-33.

5. Kalman CM, Laskin OL. Herpes zoster and zosteriform herpes simplex virus infections in immunocompetent adults. *Am J Med.* 1986;81(5):775-778.

6. Helgason S, Sigurdsson JA, Gudmundsson S. The clinical course of herpes zoster: a prospective study in primary care. *Eur J Gen Pract.* 1996;2(1):12-16.

7. Opstelten W, van Wijck AJ, Stolker RJ. Interventions to prevent postherpetic neuralgia: cutaneous and percutaneous techniques. *Pain.* 2004;107(3):202-206.

8. van Loon AM, van der Logt JT, Heessen FW, Heeren MC, Zoll J. Antibody-capture enzyme-linked immunosorbent assays that use enzyme-labelled antigen for detection of virus-specific immunoglobulin M, A and G in patients with varicella or herpes zoster. *Epidemiol Infect.* 1992;108(1):165-174.

9. Yu AL, Costa JM, Amaku M, et al. Three year seroepidemiological study of varicella-zoster virus in Sao Paulo, Brazil. *Rev Inst Med Trop Sao Paulo.* 2000;42(3):125-128.

10. Behets F, Kashamuka M, Pappaioanou M, et al. Stability of human immunodeficiency virus type 1 antibodies in whole blood dried on filter paper and stored under various tropical conditions in Kinshasa, Zaire. *J Clin Microbiol.* 1992;30(5):1179-1182.

11. McDade TW, Stallings JF, Angold A, et al. Epstein-Barr virus antibodies in whole blood spots: a minimally invasive method for assessing an aspect of cell-mediated immunity. *Psychosom Med.* 2000;62(4):560-567.

12. Opstelten W, Van Wijck AJ, Van Essen GA, et al. The PINE study: rationale and design of a randomised comparison of epidural injection of local anaesthetics and steroids versus care-as-usual to prevent postherpetic neuralgia in the elderly [ISRCTN32866390]. *BMC Anesthesiol.* 2004;4(1):2.

13. van Wijck AJ, Opstelten W, Moons KG, et al. The PINE study of epidural steroids and local anaesthetics to prevent postherpetic neuralgia: a randomised controlled trial. *Lancet.* 2006;367(9506):219-224.

14. Sriwatanakul K, Kelvie W, Lasagna L, Calimlim JF, Weis OF, Mehta G. Studies with different types of visual analog scales for measurement of pain. *Clin Pharmacol Ther.* 1983;34(2):234-239.

15. Whitley RJ, Weiss HL, Soong SJ, Gnann JW. Herpes zoster: risk categories for persistent pain. *J Infect Dis.* 1999;179(1):9-15.

16. De Swart RL, Nur Y, Abdallah A, et al. Combination of reverse transcriptase PCR analysis and immunoglobulin M detection on filter paper blood samples allows diagnostic and epidemiological studies of measles. *J Clin Microbiol.* 2001;39(1):270-273.

17. Kido S, Ozaki T, Asada H, et al. Detection of varicella-zoster virus (VZV) DNA in clinical samples from patients with VZV by the polymerase chain reaction. *J Clin Microbiol.* 1991;29(1):76-79.

18. Nahass GT, Mandel MJ, Cook S, Fan W, Leonardi CL. Detection of herpes simplex and varicella-zoster infection from cutaneous lesions in different clinical stages with the polymerase chain reaction. *J Am Acad Dermatol.* 1995;32(5 Pt 1):730-733.

19. Fleming DM, Cross KW, Cobb WA, Chapman RS. Gender difference in the incidence of shingles. *Epidemiol Infect.* 2004;132(1):1-5.

20. Gilden DH, Dueland AN, Devlin ME, Mahalingam R, Cohrs R. Varicella-zoster virus reactivation without rash. *J Infect Dis.* 1992;166(Suppl 1):S30-S34.

21. Sauerbrei A, Eichhorn U, Schacke M, Wutzler P. Laboratory diagnosis of herpes zoster. *J Clin Virol.* 1999;14(1):31-36.

22. Eaton RB, Petersen E, Seppanen H, Tuuminen T. Multicenter evaluation of a fluorometric enzyme immunocapture assay to detect toxoplasma-specific immunoglobulin M in dried blood filter paper specimens from newborns. *J Clin Microbiol.* 1996;34(12):3147-3150.

23. Spielberg F, Critchlow C, Vittinghoff E, et al. Home collection for frequent HIV testing: acceptability of oral fluids, dried blood spots and telephone results. HIV Early Detection Study Group. *AIDS.* 2000;14(12):1819-1828.

24. Judd A, Parry J, Hickman M, et al. Evaluation of a modified commercial assay in detecting antibody to hepatitis C virus in oral fluids and dried blood spots. *J Med Virol.* 2003;71(1):49-55.

25. Dahl H, Marcoccia J, Linde A. Antigen detection: the method of choice in comparison with virus isolation and serology for laboratory diagnosis of herpes zoster in human immunodeficiency virus-infected patients. *J Clin Microbiol.* 1997;35(2):347-349.