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Herpes Zoster--Eye Complications: Rates and Trends

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Abstract

Purpose—To provide population based data on the risk, types and outcomes of eye involvement in herpes zoster (HZ).

Methods—A cohort study based on medical record review of patients diagnosed with HZ between January 1, 1980 and December 31, 2007. HZ was confirmed by typical rash and symptoms or laboratory testing and eye involvement was confirmed by ophthalmologists' evaluation. Information was collected on all eye diagnoses, all HZ eye related visits, treatments, procedures and outcomes.

Results—Of the 2035 individuals with HZ in any dermatome, 184 patients (9.0%) had eye involvement. Mean age of the 184 was 62.6 with 5 cases in patients <21. Overall, 6.5% were immune suppressed at the time of the eye complications. The rate of increase of HZ eye involvement was 23% by decade from 1980 to 2007.

Common eye complications were keratitis (76.2%), uveitis/iritis (46.6%) and conjunctivitis (35.4%). Recurrent keratitis and recurrent iritis/uveitis occurred in 6.9% and 7.4% respectively. Outcomes included six (3.3%) patients with new vision decrements to 20/200 or worse. Two individuals had successful corneal transplants. Another six (3.3%) individuals had lid ptosis that affected vision including one elderly woman with a permanent unilateral tarsorrhaphy. Severe HZ eye pain was reported to be directly responsible for one unsuccessful suicide attempt. No one developed ARN. A mean of 10.8 HZ eye visits per HZ patient with eye involvement were reported over a mean of 308 days.

Conclusion—Eye complications are common, result in significant health care utilization and in permanent vision decrement in about 6.6% of individuals with HZ eye involvement. Most health care utilization and long term adverse outcomes were in patients in whom administration of HZ prevention with the zoster vaccine would be possible.

Background

Herpes zoster (HZ) is an increasingly common condition in all age groups but most common in adults age 50 and older.[1–6] Increased risk for developing HZ is associated with immunosuppression from pharmacology therapy and diseases such as AIDs and mostly commonly with the immunosenescence of aging.[7] Acute reactivation of the zoster virus

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resulting in shingles is associated with significant adverse health, decreased quality of life and cost burdens. [1,2–10] Part of that burden is due to the HZ complications that occur in about 20% of HZ cases.[1,5] Post herpetic neuralgia (PHN) which is the most common complication has numerous publications of epidemiology and costs related studies.[4,11–14] Yet, HZ ophthalmicus with eye complications, the second most common HZ complication has limited numbers of epidemiology studies and almost no population-based publications could found.[1,5,15–24]

The published HZ eye studies are complicated by confusion and misunderstanding regarding the definition of herpes zoster ophthalmicus (HZO) which occurs with or without eye involvement. However, this distinction is often unclear in published studies, lumping all studies of HZO with or without eye involvement together when assessing occurrence rates and outcomes.[17,25,26] Beyond the confusion with definitions, many publications of HZ eye complications are case reports or limited to patients seen in specialized setting such as an academic ophthalmology clinic. [27–31] Reports of time trends in HZ complications[1] are rare and we found only one study that reported population-based changes in occurrence rates and outcomes of HZO before and after the introduction of antiviral medications.[16]

Within the past six years, a vaccine has been approved for the prevention of herpes zoster (HZ) in older immune competent adults.[32–34] To adequately understand the impact of that vaccine it is important to have baseline information on the HZ burden including the burden associated with common complications. This study is designed to provide recent data for HZ eye complication rates while also examining the 25 year temporal trends of HZ eye complications in a community population.

Methods

This is a cohort study of all patients in Olmsted County, MN with a confirmed HZ diagnosis from 1980 to 2007 using medical records review. Results reported are the rates of HZ affecting the eye including the physician documented type of eye involvement, duration of complications, health care utilization for HZO and procedures associated with HZ eye complications.

Setting

Olmsted County, Minnesota provides a population setting in which HZ occurrence and progression to complications can be studied due to the resources of the Rochester Epidemiology Project (REP). The REP is a unique resource that links and indexes the records of virtually all providers of medical care to Olmsted County residents.[35–38] This linkage system provides investigators the ability to electronically search for a specific diagnosis and to identify all patients who received that diagnosis in a particular time period. Once patients with a diagnostic code of interest have been identified, investigators may then retrieve and review all medical records for each identified patient. Medical records including details of every outpatient visit to offices, clinics, and emergency departments, as well hospitalizations and all correspondence concerning each patient are available from all sources of medical care within the county. Previous studies have shown that over 98% of all care provided to Olmsted County residents is provided within the county and therefore retrievable by REP.[39] Thus, the REP provides population-based medical data.

Subjects for potential inclusion

All Olmsted County, Minnesota children and adults, beginning at birth, who had a diagnostic code of HZ or an HZ complication identified in their medical record between January 1,1980 and December 31, 2007 and have not refused research authorization

(required by Minnesota statute) were included for medical record review. To date 95% of the Olmsted County residents have not refused research authorization.[40]

The medical records of potential HZ patients were reviewed to confirm the diagnosis of acute HZ and identify the exact timing of the diagnosis. The criteria for confirmation of the HZ diagnosis have been reported previously.[1] One or more of the following were required to confirm the HZ diagnosis:

- Physician confirmed diagnosis of HZ with typical rash and pain
- Signs or symptoms consistent with HZ: acute onset of dermatomal pain and vesicular rash
- Signs or symptoms consistent with HZ complication and laboratory tests (viral culture, PCR, DFA, or other) consistent with varicella zoster virus (VZV) infection.

From these confirmed HZ cases, the cases with eye involvement were identified. The cases studied are not those with HZ ophthalmicus which often refers to the dermatome of involvement, but only those with ophthalmologist confirmed eye involvement. The medical records of patients assessed for eye involvement were followed for at least two weeks after the onset of the rash and initial assessment since eye involvement can appear after the initial examination and HZ diagnosis. If the ophthalmologist's medical record note did not say specifically herpetic eye involvement but gave no other diagnosis and prescribed therapy---topical anti-viral or steroids--the case was coded as HZ eye involvement. When eye cultures were done they were not required to be positive for VZV since many cultures do not produce any positive results. However, if the culture was positive for herpes simplex and not herpes zoster, the case was removed from the data set of HZ cases. All cases with documented eye involvement had review of their medical records for at least one year after day of HZ diagnosis, and for those with more than one year of eye involvement, until six months after the last visit that discussed any HZ eye symptoms including resolution of HZ eye involvement.

Medical records abstraction

One of three experienced nurse abstractors collected data directly from the paper or electronic medical records associated with each visit for HZ of the eye for each patient. For quality assurance 5% re-abstraction was completed and reviewed that identified agreement of greater than 95%.[41] The information collected from each HZ-eye related visit included: the visit site, the physician specialty, recorded diagnoses (keratitis, iritis, corneal scarring, etc), procedures related to the eye, medications prescribed, assessment of vision, and assessment of pain or discomfort. Demographic data abstracted included vital status as well as birth date, gender, race and highest educational level attained.

Assessment of the patient's immune status at the time of the HZ episode was done by recording the presence of any of a list of diseases and drugs that are associated with immune suppression including HIV, AIDS, actively treated malignancies (systemic chemotherapy only), all hematological malignancies and any other type of immune suppressive therapy such as that given for rheumatoid arthritis or solid organ transplant patients.[1] Cortico-steroid medications were considered immunosuppressive if they were given at levels equivalent to 10mg of prednisone daily. If none of the conditions or medication types listed above were documented at the time of or during the year prior to the HZ eye diagnosis, the patient was assumed to be immune competent.

Data analysis

Simple frequencies were calculated for the overall time period for rates of HZO with eye complications and the frequencies of specific types of eye complications among those with HZO with eye complications. Where appropriate, frequencies were compared using Chi-squared tests, and means were compared with two-sample t-tests. Age specific rates of eye complications in the population were computed using U.S. census values. A linear time trend was fit to the rates using Poisson regression.

Results

Of the 7370 patients with confirmed HZ, 184 had 189 episodes of HZ with eye involvement between January 1, 1980 and December 31, 2007. One subject had two episodes during the period and two subjects had three separate episodes of HZ with eye involvement during the study period.

The 184 affected individuals included 107 women (58.2%) and 77 men (41.8%). This was similar to the overall gender distribution of the HZ cases during this time (58.6% women and 41.4% men, $p = 0.95$) The age at diagnosis of HZ with eye complications ranged from 16 to 101 years with only five individuals less than 21 years of age at the time of the HZ eye diagnosis. One of these five patients was immune compromised at the time of the HZ eye complication. The mean age was 62.6 (s.d.19.2 years) compared with the mean age of 52.0 (s.d.23.9, $p < 0.0001$) for all individuals with HZ during this time period. Of the 184 individuals with HZ eye complications, 12 individuals were immune compromised (6.5%of the 184 individuals with HZ eye complications) during 14 episodes overall (7.4% of the 189 episodes). The majority of the immune compromised individuals (8 of 14, 57.1%) were less than age 65 years at the time of the episode.

While eye complications were more common among those aged 65 and older compared to those less than 65 in all decades studied, there was no temporal trend in percent of HZ cases with eye involvement. (Table 1) Overall, the rate of HZ cases increased by 23% per decade in all age groups thereby resulting in more absolute numbers of eye complications in succeeding decades from 1980 through 2007 ($p = 0.02$)..

Types of eye involvement

Individuals with HZ eye involvement had a number of eye related diagnoses (Table 2.) with keratitis (76.2% of all individuals with eye involvement), uveitis/iritis (46.6% of all) and conjunctivitis (35.4% of all) being the most common. One immune competent individual with eye involvement died of HZ encephalitis. Of those who were immune compromised at time of diagnosis (n=14), three had conjunctivitis only, five had keratitis, one recurrent keratitis, and two had iritis, one case of which was recurrent. Overall 33 individuals (18% of the 185) had only conjunctivitis. Recurrent keratitis (6.9% of all) and recurrent iritis/uveitis (7.4% of all) were not uncommon and in all cases occurred 3 or more months following the initial episode (range 3.1 to 13.0 months). Scleritis/episcleritis occurred in 10.6% of individuals with HZ with eye involvement. No one progressed to acute retinal necrosis (ARN). Corneal ulcerations were reported in 4.8% of all individuals but corneal scarring was identified in 10.1%. Vision altering effects such as cataracts (from HZ, 3.2%), diplopia 2.6%, blurred vision 3.2%, decreased vision 3.7% and eye lid ptosis 7.9% often resolved during the healing process. A total of 13.2% (n=24) of the patients with HZ eye involvement had new increased intra-ocular pressure diagnosed during active HZ eye disease, with 92% of these episodes associated with steroid ophthalmic drop use of 30 days or more. All but 2 appeared to resolve following the discontinuation of the steroid drops.

Not all individuals had eye involvement diagnosed on the initial visit to the ophthalmologist and several types of complications (e.g. recurrent uveitis and increased intra-ocular pressure) were first recorded weeks to months after the initial HZ diagnosis. No temporal change in rate of recurrent problems was found but the small number of recurrences per time period could have masked modest changes.

Many individuals had complete resolution of the HZ eye involvement. Adverse outcomes included reduced vision related to the eye itself sufficient to interfere with activities in six individuals (3.3%). Six additional individuals had lid ptosis that interfered with vision including one with a permanent surgical lid closure. Another two individuals had corneal scarring that resulted in corneal transplant. Several people reported eye pain but the severity and duration of eye related pain was difficult to extract from the medical records. One individual had very severe ongoing eye pain (> nine months duration) that resulted in a suicide attempt. The patient was hospitalized and both the suicidal ideation and pain were treated intensively.

Health care utilization for HZ eye-related problems

The number of HZ eye related visits per individual ranged from 1 to 44 with a mean of 10.8 visits (s.d. 8.0). All individuals with HZ eye complications had at least one visit to an ophthalmologist, with the number of ophthalmologist visits ranging from 1 to 38 with a mean of 8.0 visits (s.d. 7.1). Of the total, 119 individuals received oral antiviral medications, 8 received antiviral eye drops and 5 received both. Most of those not receiving oral antiviral medications were during the earliest portion of the time period. A total of 32 individuals were hospitalized during the HZ episode and had a range of 0 to 14 eye related visits during the hospitalizations [mean of 2.77 (s.d. 3.63)]. When considering only outpatient visits the mean number of eye visits per case of HZO with eye involvement fell to a mean of 7.67, range 0 to 38 (s.d. 7.04).

The duration of specific ophthalmology follow-up visits ranged from 1 day with a single eye visit for 23 individuals to 7.9 years with a mean of 209 days (s.d. 349). For 33 of the HZ eye episodes (17.4% of all), the follow up period for the eye complication lasted longer than one year from the date of diagnosis of the HZ eye involvement.

Individuals were hospitalized during 32 of the 189 HZ episodes that included eye involvement (16.8%) although not usually for the eye complications. Only 6 hospitalizations appeared to be related to HZ eye complications including further evaluation and treatment of severe eye pain in 3 individuals, a suicide attempt associated with severe and persistent eye pain and IV antiviral treatment for 2 immune compromised individuals with HZ eye involvement. All individuals that were immune compromised at the time of the HZ eye involvement were hospitalized for intravenous antiviral therapy, though only 2 were specifically stated to be related just to the eye concerns.

Procedures related to the HZ eye complications were uncommon and consisted almost entirely of punctal plugs (7 individual with 14 plugs, 42% of cases) for dry eye problems. One individual had a permanent thermocautery procedure to the left puntum. Five tarsorrhaphies were done in four individuals (2% of all individuals). One of these was a permanent tarsorrhaphy for lid laxity and vision loss in an 87 year old woman who also experienced a stroke five days after the onset of the HZ that resulted in sustained muscle paralysis of the same side of the face affected by the HZ. The most unusual procedure was a series of 2 supra-orbital foramen injections of alcohol completed in 2002 after confirmed ongoing total vision loss in the R eye and uncontrollable HZ related eye pain. Three other individuals received a reported nine peri-orbital injections for ongoing zoster related eye

pain. Four individuals had CTs of the orbit on the affected side. Two MRIs were ordered for further evaluation.

Discussion

Herpes zoster eye complications were common during this 28 year period and incidence rates of eye complications among HZ cases increased 23% between 1980 and 2007. Health care utilization was extensive for HZ eye complications with an average of more than 8 visits over a six month or longer period. One in 15 people with eye complications had one or more eye procedures directly related to the HZ. One in ten of the patients had recurrences or onset of keratitis or uveitis delayed for four or more weeks after the HZ was diagnosed. Significant visual loss occurred in 6.6% of the individuals with HZ eye complications.

The rate of increase of eye complications within the population with HZ becomes even more significant when put in the context of studies of HZ trends over the same 30 years. In this same Olmsted County, MN population HZ incidence was reported to have increased 1.7 fold from 1980 through 2006.[1] Other shorter term studies have also reported increases in HZ incidence.[42,43] The overall numbers of HZO cases with eye involvement combines both the overall increase in HZ cases and the increase in the rate of HZO with eye involvement within those HZ case (1.70 fold increase in HZ X 1.23 increase in HZO with eye involvement in HZ = 2.1 fold increase in numbers of HZO eye cases per year between 1980 and 2007).

The collection of published HZ eye studies are complicated by confusion in the definition of Herpes Zoster Ophthalmicus (HZO) which is stated to be a typical vesicular eruption affecting the distribution of the ophthalmic division of the trigeminal nerve which can sometimes involve the eye.[17,26] Investigators often report on HZO without regard to eye involvement.[15,16,23] Other publications report on HZO as HZ only with confirmed eye involvement.[1,21,22,26] In our study, we found more than three times as many cases of HZ considered to be in the dermatome for HZO than cases of HZO that actually involved the eye by ophthalmologists' confirmation. Similar rates appear from the literature of developed countries or when a population based approach was taken.[16,17,19,25,34,43] Having a clear definition of HZO as either HZO with eye involvement or all cases regardless of eye involvement is mandatory for accurately assessing and reporting the continuing epidemiology and natural history of HZ and its complications. We recommend that the terminology become standardized as HZO with eye involvement or HZO without eye involvement to clarify HZO terminology in all future reports.

In 2003, Severson et al published a study of HZO in the same Olmsted County population including the years 1976 to 1998 to compare rates of different types of complications and outcomes before and after the use of anti-viral oral medications for HZ treatment.[16] The information is reported as the rates of complications of all individuals with zoster in the dermatome rather than only those with eye involvement as we report. As anticipated the absolute rates reported are different due to the difference in the definition for the denominator. However, the relative frequency of the complications is very similar to those we report. Severson et alrates of uveitis, scleritis and increased intraocular pressure are 0.33 to 0.37 the rates we report ($p > 0.10$). However, Severson does report a higher relative rate of keratitis (0.46 of the rate we report). As in our data, Severson et al report no cases of optic neuritis or ARN. The Severson report does not discuss health care utilization rates.

Many of the published reports of HZO are case reports [25,27,29,44–54] or studies based in unique settings such as the emergency department[28] which primarily discuss presentation and acute therapy. Liesegang published a literature review of HZO which included all cases

of HZ in the fifth cranial nerve with or without eye involvement.[17] The paper did not identify the numerical risk of HZO or HZO with eye involvement.

One of the only HZO outcome studies is from the Department of Ophthalmology at Glostrup University in Copenhagen where 110 cases of HZO with eye involvement were seen over a seven year period and 5.5% had non-pain neurological complications.[44] No denominator is given for the total number of HZ cases and eye outcomes are not discussed. Another study from Japan demonstrates an association with VZV viral load in the aqueous humor and damage to the iris.[45] This paper provides no epidemiological data. Two British reports provide data on HZO and the varicella zoster virus as the most common cause (10 of 19, 56%) of acute retinal necrosis (ARN) in a population based study in the British Ophthalmological Surveillance Unit.[55,56] The studies provide no data to determine rates of HZO with eye involvement or for population rates of ARN.

Cordero-Coma and colleagues present a nice review of the different forms and consequences of herpetic retinal inflammation which is useful to identify potential adverse outcomes but does not provide information on frequency or temporal trends of those outcomes.[57] Nithyanandam et al present outcomes from a convenience sample of patients with HZO and look for associations between eye outcomes and the severity of the initial HZ eruption.[26] They found that the severity of the HZO eruption (rash) in the first cranial nerve dermatome was associated with not only eye involvement but also reduced vision outcomes. Since our study was based on retrospective review of medical records we have no reliable information on the severity of the HZ rash to compare to outcomes.

Several recent studies of HZO have also come from convenience samples but in communities and countries with high rates of HIV, AIDS and active tuberculosis that can significantly increase the risk of HZ reactivation and shift the occurrences of HZ and therefore HZO to younger age groups.[58] Ghaznawi et al report on 112 cases of HZO that presented for eye care and show that the rate of those was the same in ages less than 60 years and those 60 and older. This data is not population based and comes from a country with much higher rates of HIV, AIDS and active Tuberculosis which were very common co-morbidities in Ghazwani's group of age less than 50 years. [21] Gupta's study of 18 young adults with HZO eye involvement is also drawn from a population[22] that is comparable to that of Ghazwani's population but very different from the Minnesota population we studied. Puri presents findings on 68 cases of HZO sent for eye care.[23] Overall 78% had some type of eye involvement many of which (45.8%) were lid or adnexal findings that are not reported in other HZO studies and are likely to have raised the estimate of eye involvement in HZO.[23] These important studies add information primarily to the global issue of HZO but cannot be compared to our US population based study.

As with all retrospective studies, our study is limited by the information documented in the medical record. It is possible that some individuals with HZO did not have an eye evaluation and were not referred for eye evaluation. Furthermore, not all people with HZ may make a health care visit during the episode. Therefore, we may under estimate the rate of HZ eye involvement. Recurrence rates and timing for iritis and even conjunctivitis can be difficult to discern during any HZO eye complication episode.

Information in the medical record is not always clear regarding resolution of one episode before another visit occurs unless the diagnosis is clearly stated as recurrent iritis or recurrent conjunctivitis. A few Olmsted County residents may seek specialty care outside of Olmsted County but this has been estimated to be less than 2% of all care.[39] The denominator we use for prevalence estimates of HZ eye involvement in the total population is from the county level census data. Olmsted County is a growing community and therefore

the estimates of total population were interpolated for each year and are likely to be close but not exact.

Some cases of HZ may never be correctly diagnosed or coded in the data systems. While this is certainly possible in cases where only a single HZ visit is made, it is unlikely that multiple visits will all be miscoded.[59] If only one visit is made that receives an HZ code with other follow up visits not receiving the HZ or any visit receiving an HZ eye code, our medical record review allowed us to identify the visits that were not properly coded.

This is a true population based study rather than reflecting only the insured or covered population usually available through MCO or HMO populations. The Olmsted County population is similar to the total US white population in age and gender distribution. However, the Olmsted County population has a smaller proportion of racial and ethnic minority residents, a slightly higher education level, and a lower poverty level compared to the general US population. In addition, a higher proportion of the Olmsted County population is employed in a health service field compared to the rest of the US population. [35–37]

HZ eye complications affected about 9% of this group of individuals studied in Olmsted County, MN. That translates to about 9% of the nearly one million new HZ cases each year (90,000 HZ eye complications per year) The rates are increasing and outcomes while usually good can result in prolonged requirements for medical eye care and reduced vision associated with significant health care burden. HZ and therefore HZO is potentially preventable after administration of the zoster vaccine that is reported to reduced the rate of HZ by an average of 51% in vaccine eligible adults aged 60 years and older[60] with higher rates of protection in those age 50 to 59 years.[61,62] While not currently preventable, eye complications of HZ in younger individuals should still be recognized as a potential risk factor for adverse outcomes and addressed appropriately with specialty eye care.[63,64]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Age stratified incidence rates of HZ eye complications by time period

Age in years	1980–1989 Rate/10,000 person-years (CI_{95})	1990–1999 Rate/10,000 person-years (CI_{95})	2000–2007 Rate/10,000 person-years (CI_{95})
0 through 64	0.29 (0.18–0.42)	0.296 (0.20–0.42)	0.45 (0.32–0.61)
65 and older	2.65 (1.63–3.78)	2.28 (1.50–3.32)	3.44 (2.47–4.67)

Poisson regression for increase in rates over time (23% increase, p = 0.02)

Table 2

Frequency of diagnoses* associated with HZ eye complications. *(Descending order of frequency)

	Total	F	M
Keratitis	144 (76.2%)	84 (77.1%)	60 (75.0%)
Iritis, uveitis	88 (46.6%)	53 (48.6%)	35 (43.8%)
Conjunctivitis	67 (35.4%)	40 (36.7%)	27 (33.8%)
Severe eye pain:	27 (14.3%	18 (16.5%)	9 (11.3%)
Increased intraocular pressure	25 (13.2%)	16 (14.7%)	9 (11.3%)
Scleritis/episcleritis	20 (10.6%)	12 (11.0%)	8 (10.0%)
Corneal scarring	19 (10.1%)	16 (14.7%)	3 (3.8%)**
Ptosis	15 (7.9%)	11 (10.1%)	4 (5.0%)
Corneal ulceration	9 (4.8%)	8 (7.3%)	1 (1.3%)
Decreased vision:	7 (3.7%)	4 (3.7%)	3 (3.8%)
Blurred vision:	6 (3.2%)	5 (4.6%)	1 (1.3%)
Cataracts (from HZ)	6 (3.2%)	5 (4.6%)	1 (1.3%)
Diplopia	5 (2.6%)	3 (2.8%)	2 (2.5%)
Recurrent inflammation:			
Recurrent uveitis:	14 (7.4%)	10 (9.2%)	4 (5.0%)
Recurrent keratitis:	13 (6.9%)	9 (8.3%)	4 (5.0%)

*Individuals may have more than one diagnosis

**P = 0.03 all others p > 0.05