SHORT COMMUNICATION

Varicella-zoster Virus Infections in Patients with Hospital-diagnosed Atopic Dermatitis

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Patients with atopic dermatitis (AD) are at increased risk of disseminated herpes simplex (1) but population-based studies on the course of varicella-zoster virus (VZV) infections are limited (2, 3). Primary infections with varicella and reactivation as zoster are both vaccine-preventable (4). However, many countries, including Denmark, have not implemented routine or targeted vaccination, partly due to insufficient data on the disease burden (4). To inform vaccine policy, we conducted a nationwide Danish cohort study using linked registry data to describe the epidemiology of VZV infections in hospital-diagnosed AD.

MATERIALS AND METHODS

Using the Danish National Patient Registry (5), we identified people diagnosed with AD from an admission (recorded nationwide since 1978) or a hospital outpatient clinic or emergency department (available since 1995) from 1 January 1979, to 30 June 2016. We followed patients until varicella or zoster, emigration, death, or 30 June 2017. As VZV infections are not routinely registered in general practice, we were limited to cases treated in the hospital sector. However, for zoster, we attempted to capture primary care diagnoses by including first-time antiviral prescriptions at tablet doses used for zoster at age ≥40 as a proxy (5, 6). Analyses of varicella excluded patients with previous varicella or zoster.

To estimate the burden of the most severe infections, we considered hospitalizations separately, estimated the length of hospital stay, and identified complications within 4 weeks after diagnosis. For bacterial superinfection, we supplemented diagnoses with antibiotic prescriptions. We defined post-herpetic neuralgia (PHN) as a hospital diagnosis or initiation of a drug for PHN within 90–365 days after zoster.

To identify predictors of VZV infection, we performed a secondary nested case-control analysis comparing AD patients with varicella or zoster (cases) with AD patients without such diagnosis (controls) matched (1:1) by birth year, sex, and time since AD diagnosis. We included AD severity, asthma, rhinitis, severe immunosuppression, solid cancer, mood disorder, and education level as independent variables (2, 6–9). We categorized severity based on treatment in the year before infection as severe (systemic therapy), moderate (topical corticosteroid or calcineurin inhibitor treatment), or mild (remaining patients). Table SI provides variable definitions.

Statistical analysis

We computed crude and age-standardized rates, quartiles for length of stay, and the complication prevalence for varicella and zoster separately. We estimated the cumulative incidence proportion since AD diagnosis, treating death as a competing risk. For zoster, we also performed landmark analyses delaying follow-up start to age 18, 40, and 50 in AD patients who were alive and event-free by that age. We estimated the association between potential risk factors and VZV infection in unadjusted (bivariate) and adjusted (all variables) conditional logistic regression.

RESULTS

We included 46,875 and 47,081 AD patients in the analysis of varicella and zoster, respectively (median age 5.8 years at AD diagnosis; 50.7% female; Table SII**)**. The varicella hospital diagnosis rate was 29.5/100,000 person-years, higher in males than females (1.3:1) (**Table I**). The hospitalization rate was 16.2/100,000 person-years. The overall varicella rate decreased substantially with age at first AD diagnosis. In the youngest age group, 0.85% were hospital diagnosed, and 0.48% were hospitalized with varicella within 5 years after diagnosis (Fig. S1, Table SIII). Complications were registered in 47.1% of cases (63.8% of inpatients), and the median length of stay was 3 days (Table I).

The zoster rate was 151.7/100,000 person-years overall and 7.2/100,000 person-years for hospitalizations (Table I). The overall rate was highest in females (1.3:1), while hospitalizations were more common in males (1:2.2). After 35 years, 7.3% had been diagnosed, and 0.21% had been hospitalized with zoster (Fig. S1, Table SIII). In landmark analyses, 41.8% of 40-year-olds and 22.8% of 50-year-olds with AD had zoster by age 75 (Table SIV, Fig. S2). Complications were observed in 22.3% (45.5% of inpatients), and the median length of stay was 6.5 days (Table I).

The case-control analysis was infeasible for varicella. Increasing AD severity, asthma, severe immunosuppression, and higher educational level predicted zoster, while rhinitis and mood disorders were associated with slightly reduced odds (Table SV).

DISCUSSION

A previous Danish study reported a varicella hospital diagnosis rate of 26/100,000 person-years and a hospitalization rate of 11/100,000 person-years among 0–17-year-olds in the general population during 2010–2015 (3). The median length of stay (2 days; IQR: 1–4) was slightly shorter than in our population. Although methodological differences hamper direct comparison of rates, we can roughly estimate that among patients with AD aged 0–17 years on 1 January each year during 2010–2015, an average of 40.4/100,000 were diagnosed and 16.1/100,000 hospitalized with varicella within a year. This confirms

Table I. Epidemiology of varicella and herpes zoster in people with hospital-diagnosed atopic dermatitis

	Varicella		Zoster	
Factor	Any hospital diagnosis[a]	Hospitalizations	Any diagnosis[b]	Hospitalizations
Events, *n* (%)	209 (0.4%)	115 (0.2%)	1,075 (2.3%)	51 (0.1%)
Duration of follow-up, PY	709,111	709,111	708,758	708,758
Crude rate per 100,000 PY	29.5 (25.6–33.8)	16.2 (13.4–19.5)	151.7 (142.7–161.0)	7.2 (5.4–9.5)
Age-standardized rate per 100,000 PY, overall[c]	6.4 (4.5–8.9)	3.7 (2.3–5.6)	517.6 (498.9–536.8)	15.9 (12.7–19.6)
Females[c]	5.6 (3.2–9.1)	3.3 (1.5–6.1)	580.9 (553.0–609.7)	10.1 (6.8–14.6)
Males[c]	7.2 (4.4–11.1)	4.1 (2.1–7.3)	452.9 (428.1–479.8)	21.8 (16.6–28.0)
Crude rate per 100,000 PY, by age at first AD diagnosis				
0–5 years	52.4 (45.4–60.2)	29.0 (23.8–34.9)	15.6 (11.9–20.1)	4.2 (2.4–6.8)
6–9 years	2.7 (0.3–9.9)	2.7 (0.3–9.9)	54.3 (38.8–74.0)	8.1 (3.0–17.7)
10–17 years	6.7 (2.2–15.6)	1.3 (0.0–7.4)	111.2 (88.5–137.8)	6.7 (2.2–15.6)
18–40 years	2.2 (0.4–6.3)	1.4 (0.2–5.2)	367.1 (335.7–400.7)	10.2 (5.6–17.2)
≥ 40 years	NA[d]	NA[d]	984.2 (888.9–1086.9)	25.2 (12.1–46.4)
Complications, *n* (%)[e]	73 (47.1)	44 (63.8%)	238 (22.3)	20 (45.5%)
Nervous system	7 (< 4.5)[d]	< 7 (10.1)	17 (1.6)	< 5 (< 11.4)[d]
Bacterial	44 (28.4)	24 (34.8)	175 (16.4)	14 (31.8)[d]
Immune-mediated	< 5 (< 3.2)[d]	< 5 (7.3)[d]	< 5 (< 0.5)[d]	0
Ocular or otological	0	0	33 (3.1)	< 5 (< 11.4)[d]
Disseminated infection	< 5 (< 3.2)[d]	< 5 (7.3)[d]	< 5 (< 0.5)[d]	0
Other/unspecified	8 (< 5.2)[d]	< 8 (< 11.6)	5 (< 0.5)[d]	< 5 (< 11.4)[d]
Post-herpetic neuralgia	NA	NA	22 (2.1)	< 5 (< 11.4)[d]
Length of stay, median (IQR)[f]	NA	3 (1.5–5)	NA	6.5 (2.0–21)

[a]Including inpatient, hospital outpatient, and emergency department diagnoses. [b]Including inpatient, hospital outpatient, and emergency department diagnoses and patients identified by antiviral prescriptions used for treatment of zoster. [c]Age-standardized to the 2000 Danish census. [d]Masked to preserve anonymity per rules by Statistics Denmark. [e]For varicella-zoster infections diagnosed since 1994 when the 10th revision of the International Classification of Diseases was introduced. When considering complications separately, patients could contribute to several categories. [f]For primary inpatient diagnoses. Considering all inpatient diagnoses, the median length of stay was 3 days (1–5 days) for varicella and 5 (2–21 days) for zoster. AD: atopic dermatitis; IQR: interquartile range; PY: person-years.

a substantial burden of varicella in Danish patients with AD (3), a population-based cohort study in UK primary care (2), and 2 cross-sectional US studies using self-reports (10, 11).

Population-based Western studies using primary care data report up to 60% increased relative risk of zoster depending on age and severity of AD (2, 7). Cross-sectional studies have also linked AD to zoster in the hospital setting (12, 13). We found age-standardized zoster rates twice as high as in the general Danish population for any diagnosis (5.1 vs 2.3/1,000 person-years) (6) and hospitalizations (16 vs 7.9/100,000 person-years in 1994–2012) (14). Length of stay is also longer (6.5 vs 4 days) despite younger median age (24 vs 73 years) at hospitalization (14). In 40-year-olds with AD, the 35-year risk of zoster is 42% compared with a lifetime risk of 26% at age 75 in the general population (15).

The higher rates of hospital-diagnosed VZV infections in males and of zoster overall in women are also observed in the general population (3, 6, 14). Previous studies also found that AD severity predicts zoster (2). Zoster has been linked to severe immunosuppression, asthma, and higher socioeconomic position (possibly due to health-seeking) in the general population (4, 7, 8, 14), but we could not reproduce an increased risk for rhinitis (7) and mood disorders (6).

Strengths of our study include a nationwide population-based cohort with long-term follow-up. However, we could not examine milder varicella and the exact population at risk was unclear, because primary care data were unavailable. Our prescription-based algorithm for zoster may have misclassified some cases of herpes simplex and missed untreated and younger patients (6). Closer follow-up of patients with AD may increase ascertainment of relatively milder VZV infections in the hospital setting, but we found a proportional increase in diagnoses overall and hospitalizations. The prevalence of bacterial complications was very high and may have been biased upwards if some antibiotics were prescribed on a low suspicion or as rescue packs. On the other hand, we likely missed other unregistered complications, in particular PHN.

Our results may not generalize to milder AD treated only in primary care. Also, biologics and small molecule therapies have improved AD management but were not marketed during the study. However, VZV infections will likely continue to pose a threat to patients because JAK inhibitor treatment is associated with VZV reactivation (1).

In conclusion, VZV infections and complications are common in AD. These patients might thus benefit particularly from the introduction of varicella vaccination. Furthermore, our findings could motivate prompt antiviral treatment for patients with AD presenting with varicella. We also add to the evidence suggesting that at least patients with AD who have moderate-to-severe disease, including potential candidates for systemic therapy, should be offered the zoster subunit vaccine, which is marketed for adults aged ≥ 18 years who are at increased risk of zoster.

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board approval or informed consent from subjects in registry-based studies.

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