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Characteristics and long-term prognosis of Danish patients with varicella zoster virus detected in the cerebrospinal fluid, compared with the background population.

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Summary of main points

In this nationwide, population-based cohort study in Denmark, immunosuppression and comorbidity were associated with increased risk of detection of VZV DNA in the CSF and the condition was associated with increased mortality and neurological morbidity.

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ABSTRACT

Background

Risk factors for and long-term outcomes following detection of varicella zoster virus (VZV) DNA in the cerebrospinal fluid (CSF) are unknown.

Methods

We performed a nationwide population-based cohort study of all Danish residents who had VZV DNA detected in the CSF by polymerase chain reaction (PCR) between 1 January 1997 and 1 March 2016 (VZV cohort; n = 517) and an age- and sex- matched comparison cohort from the general Danish population (n = 9823). We examined potential risk factors and mortality, neurologic morbidity, psychiatric morbidity, redemption of medicine prescribed for the nervous system and social outcomes.

Results

Prior hospital admission, redemption of immunosuppressive medicine, comorbidity and immunosuppressive conditions were associated with detection of VZV DNA in the CSF. Mortality was increased in the VZV cohort, especially during the first year of observation and among patients with encephalitis. Patients in the VZV cohort had an increased risk of dementia and epilepsy. The redemption of antiepileptics and antidepressants was increased in the VZV cohort.

Conclusions

Immunosuppression and comorbidity are associated with increased risk of detection of VZV DNA in the CSF and the condition is associated with increased mortality and neurological morbidity.

Key words

varicella zoster virus; meningitis; CNS infection

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INTRODUCTION

Varicella zoster virus (VZV) causes varicella as the primary infection. [1,2] Approximately 98% of the population in Denmark and neighboring countries have been infected with varicella during childhood. [3,4] Complications of varicella include secondary bacterial infections, hemorrhagic manifestations, pneumonitis, cerebellitis and encephalitis. [1,2,5]

After primary infection, VZV establishes a latent infection in ganglionic neurons along the neuroaxis and in enteric and autonomic ganglia. [1] Reactivation often manifests as herpes zoster [6,7] and may lead to detection of VZV in the cerebrospinal fluid (CSF), which is associated with neurologic manifestations such as cranial nerve palsies, polyneuropathy, meningoencephalitis, myelopathy, and VZV vasculopathy. These neurologic manifestations can occur with and without herpes zoster. [6–8]

To what extent inflammation and VZV DNA in the CSF might accompany uncomplicated herpes zoster without concurrent meningeal or neurologic symptoms is unknown. [9,10]

Polymerase chain reaction (PCR) is the primary analysis to detect viral DNA of the CSF when VZV is assumed to cause neurologic disease. [5] Long-term follow-up studies of prognosis in patients following detection of VZV DNA in the CSF are needed to guide patient management.

We aimed to study immunosuppression and comorbid conditions as risk factors for detection of VZV DNA in the CSF as well as the prognosis after detection of VZV DNA in the CSF in terms of mortality, neurologic and psychiatric morbidity, prescription of medicine used for the nervous system and social functioning.

METHODS

Setting

Denmark has a population of approximately 5.8 million individuals. [11] Tax-supported health care is provided free of charge to all Danish residents. [12]

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Data Sources

We used a population-based nationwide cohort design, as described previously. [13–17] We tracked individuals in Danish national health and administrative registries by use of the unique 10-digit personal identification number, assigned to all Danish residents at birth or upon immigration. [12,18–25] Patients who had VZV DNA detected in the CSF by PCR were identified from data files from all Danish microbiology laboratories that performed this test between 1 January 1997 and 1 March 2016. We used the Danish Civil Registration System to identify the comparison cohort. [22] Additional medical and demographic data were extracted from the Danish Civil Registration System, the Danish National Patient Registry (DNPR) covering all Danish non-psychiatric and psychiatric hospitals, the Danish Cancer Registry, the Personal Income Statistics database and housing statistics from Statistics Denmark as well as the Danish National Prescription Registry. [12,18–26] Diagnoses in DNPR are coded by the attending physician according to the International Classification of Diseases, Eighth Revision (ICD-8) until 31 December 1993 and the Tenth Revision (ICD-10) thereafter – ICD 9 was never introduced in Denmark. [23]

Study Populations

Cohort of patients who had VZV DNA detected in the CSF (VZV cohort)

Patients were included in the VZV cohort, if VZV DNA was detected in their CSF by PCR during the period 1 January 1997 to 1 March 2016 and if they were Danish residents at time of study inclusion. The date of study inclusion was defined as the first date of lumbar puncture, which lead to detection of VZV DNA in the CSF. We categorized patients in the VZV cohort into one of 4 disease categories according to ICD-10 codes made in the DNPR during the hospital contact related to study inclusion: 1) *encephalitis*, 2) *meningitis* (and no encephalitis), 3) *herpes zoste*r (and no encephalitis or meningitis) or 4) *other* (i.e. no encephalitis, meningitis or herpes zoster). Codes used for this categorization are provided in Supplementary Table 1.

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Comparison cohort from the general population

For the comparison cohort we identified all Danish residents, who were not included in the VZV cohort. From this population, we identified 19 individuals at random per patient in the VZV cohort, who had the same sex and date of birth as the patient. Persons in the comparison cohort were assigned the same date of study inclusion as the patient in the VZV cohort to whom they were matched.

Statistical analysis

Immunosuppressive and comorbid conditions

We ascertained the proportion of individuals in the VZV and comparison cohorts diagnosed with an immunosuppressive or comorbid condition each year from the latest of birth, immigration, start-up date of the registry recording the outcome of interest, or 5 years before date of study inclusion and until the earliest of the following events: 1 March 2016, death, emigration, loss to follow-up or 5 years after study inclusion. An immunosuppressive or comorbid condition was defined as hospitalization or prescription of immunosuppressive medicine in that particular year or ever being diagnosed with comorbidity or immunosuppressive disorders as defined in Supplementary Tables 2 – 4. We calculated risk differences of each outcome with 95% confidence intervals (CIs), and used conditional logistic regression to obtain crude odds ratios (ORs) with corresponding 95% CIs for the immunosuppressive and comorbid conditions mentioned above as measured 1, 2 and 5 years *before* study inclusion.

Mortality and neurologic and psychiatric morbidity

We calculated time from date of study inclusion to 1 March 2016, event of interest, death, emigration or loss to follow-up, whichever came first. We used Kaplan-Meier tables to compute the cumulative incidence of death and the cumulative incidence function to compute cumulative incidence of neurologic and psychiatric morbidity. In these analyses, death was considered

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competing risk. [27] By use of stratified Cox-regression, we computed hazard ratios (HR) as measures of relative risk of death and neurologic and psychiatric morbidity. Neurologic diseases of interest were dementia and epilepsy, whereas psychiatric diseases of interest were disorders due to psychoactive substance use, schizophrenia, mood affective disorders, anxiety, obsessive compulsive disorder and reaction to severe stress and adjustment disorders, as well as psychiatric disease overall. ICD-10 codes used to define these diseases are provided in Supplementary Table 5. The proportional hazard assumption was checked using Schoenfeld residuals. Although no violation was found, we made separate estimates for short-term (< 12 months) and long-term (>= 12 months) risks for mortality, neurologic diseases and psychiatric disease overall. The analyses of mortality and neurologic and psychiatric morbidity was stratified according to the 4 patient categories described above (encephalitis, meningitis, herpes zoster and other) and repeated in the subgroup of individuals aged 15 years or more, as patients of this age primarily suffer from reactivation of VZV [2–4,28]. Finally, the mortality analyses were repeated in a subgroup of individuals of the VZV and comparison cohorts with no immunosuppressive or comorbid conditions at time of study inclusion - matching ratio in these analyses was 1:3.

We ascertained the proportion of individuals in the VZV and comparison cohorts that were diagnosed with the neurologic and psychiatric disorders outlined above each year from immigration, birth or 5 years before date of study inclusion (whichever came last) until the earliest of the following events: 1 March 2016, death, emigration, loss to follow-up or 5 years after study inclusion. For each year, we calculated risk differences with 95% CIs.

Redemption of medicine prescribed for the nervous system

We extracted data on all redemptions of medicine used for the nervous system in Danish pharmacies according to the Anatomical Therapeutic Chemical (ATC) classification [29]. We examined the redemption of prescribed medicine used for the nervous system as a dichotomic variable (redemption of any dose versus no redemption). We examined analgesics, antiepileptics,

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psycholeptics and psychoanaleptics with corresponding sublevels of classifications according to the ATC codes provided in Supplementary Table 6.

We calculated the proportion of individuals in the VZV and comparison cohorts, who redeemed this medicine each year from 5 years before study inclusion until 1 March 2016, death, emigration, loss to follow-up or 5 years after study inclusion, whichever came first. For each year, we calculated proportion differences with corresponding 95% CIs.

Social functioning

We determined employment status, receipt of a disability pension, income, number of days of sick leave, nursing home residency and marital status each year from immigration, or start-up date of the registry recording the outcome of interest or 5 years before date of study inclusion (whichever came last) until the earliest of the following events: 1 March 2016, death, emigration, loss to follow-up or 5 years after study inclusion. For each year, we calculated differences in each outcome with 95% CIs. In these analyses, we only included individuals aged 20 – 60 years, except for the analyses of nursing home residency, in which we included individuals aged 20 years or more.

RESULTS

Description of the cohorts

We identified 517 patients for the VZV cohort of whom 249 (48%) were male and 463 (90%) were 15 years or more, and 9823 age- and sex- matched individuals for the comparison cohort (Table 1). Two hundred and twenty-seven patients (43%) were categorized as having encephalitis and 104 (20%) patients as having meningitis (Table 1). We identified 149 patients in the VZV cohort and 447 age- and sex matched individuals from the comparison cohort with no immunosuppressive or comorbid conditions. These individuals had a median age of 40 years (IQR: 25 - 58) and 54% were male.

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Immunosuppressive and comorbid conditions

More patients in the VZV cohort than individuals in the comparison cohort were admitted to hospital, redeemed immunosuppressive medicine, had comorbidity and had immunosuppressive conditions in the years leading up to study inclusion (ORs = 2.5 (95% CI: 2.0 to 3.0), 4.3 (95% CI: 3.4 to 5.6), 2.4 (95% CI: 2.0 to 3.0) and 2.6 (95% CI: 2.1 to 3.4), Table 2 and Figure 1).

Mortality and neurologic and psychiatric morbidity

Mortality was increased in the VZV cohort, with a HR of 5.42 (95% CI: 3.59 to 8.19) the first year of observation and of 1.54 (95% CI: 1.21 to 1.95) from the second year of observation (Figure 2 and Table 3). The difference in 12-year survival was 11% (95% CI: 3% to 19%). Among patients with no immunosuppressive or comorbid conditions, mortality and mortality differences were lower (Table 3 and Supplementary Figure 1). Mortality and mortality differences were higher among patients diagnosed with encephalitis than patients diagnosed with meningitis (Table 3 and Supplementary Figure 2). Mortality in the 463 patients in the VZV cohort aged 15 years or more was essentially the same as that of the entire study group (Table 3 and Supplementary Figure 3).

Patients in the VZV cohort had an increased risk of dementia and epilepsy (Table 3 and Figure 2). The proportion of individuals diagnosed with dementia was increased the year of- and following study inclusion in the VZV cohort compared with the comparison cohort. For epilepsy, this increase started already before study inclusion (Supplementary Table 8 and Supplementary Figure 4). The increase in risk of dementia and epilepsy was higher among patients diagnosed with encephalitis than patients diagnosed with meningitis but remained essentially the same when studied in the subgroup of individuals aged 15 years or more (Table 3 and Supplementary Figure 5).

There was no evidence of an increased risk of psychiatric disease in the VZV cohort (Table 3, Figure 2, Supplementary Table 9 and Supplementary Figure 6). Further, the proportion of patients in the

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VZV cohort with psychiatric diseases did not increase following study inclusion (Supplementary Table 8 and Supplementary Figure 7).

Redemption of medicine prescribed for the nervous system

In general, patients in the VZV cohort were prescribed more medicine for the nervous system than individuals in the comparison cohort, not only following-, but also prior to study inclusion (Supplementary Table 10 and Supplementary Figures 8-11). The redemption of medicine was particularly elevated in the year of study inclusion for patients in the VZV cohort. Subsequently, the level of redemption seemed to return to "baseline" for analgesics and psycholeptics, whereas the redemption of antiepileptics and psychoanaleptics including antidepressants remained increased.

Social functioning

Social function seemed to be lower among patients in the VZV cohort following study inclusion, both compared with the comparison cohort and compared with the patients' own level before study inclusion (Supplementary Figure 12). Most marked differences regarded number of sick leave days, mean income and disability pension. However, these differences were generally small and not statistically significant (Supplementary Table 11).

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DISCUSSION

In this nationwide, population-based cohort study we demonstrated that immunosuppression and comorbidity is associated with an increased risk of detection of VZV DNA in the CSF. We also demonstrated an increased mortality among patients in the VZV cohort, especially in the first year of observation, among patients with immunosuppression and comorbidity and among patients diagnosed with encephalitis. Patients in the VZV cohort also had an increased risk of dementia and epilepsy and an increased use of antiepileptics following diagnosis. There was no increased risk of psychiatric diseases in the VZV cohort, but the redemption of antidepressants increased following diagnosis.

The study design including long-term follow-up allows us to study outcomes that can be rarely addressed elsewhere. The use of national registers to capture prospectively collected data, unbiased by our study hypothesis, enables a valid comparison with the background population. Finally, we used data on prescribed medicine as an outcome. This enabled us to study less severe cases of neurologic and psychiatric diseases as a supplement to more severe cases referred to the hospital system.

Our inability to categorize patients according to CSF cell count and predefined diagnostic criteria into well-defined disease categories is a limitation of the study. Although ICD-10 codes for VZV meningitis and encephalitis have not been validated in Denmark, the access to DNHR allowed us to categorize the patients in four clinical categories.

Immunosuppression has been associated with an increased risk of herpes zoster [30,31] and with neurologic complications of VZV. [6] We extend these findings by demonstrating that hospitalization, treatment with immunosuppressive medicine, comorbidity and immunosuppressive conditions are risk factors for detection of VZV DNA in the CSF. Further, we were able to demonstrate that only a minority of patients in the VZV cohort had no known immunosuppressive or comorbid conditions.

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A recent cohort study of 92 adults with VZV encephalitis demonstrated a 3-month mortality of 11%, [32] which is comparable to the 3-month mortality observed in our study. Importantly, mortality differed according to the presence of immunosuppressive or comorbid conditions and according to whether patients were diagnosed with encephalitis or meningitis. This information will help guide individualized follow-up after detection of VZV DNA in the CSF.

In the study by Mailles et al., 15% of patients with VZV encephalitis suffered from memory impairment [33], which is higher than the 12-year risk of dementia demonstrated in our study. Memory impairment and slowness of cognitive processes were also demonstrated in the study of 9 patients with VZV encephalitis by Hokkanen et al. [34] Taken together these studies suggest that VZV encephalitis might be associated with an increased risk of dementia. Importantly, as opposed to previous studies, [33,34] we were able to compare the risk estimates among patient in the VZV cohort with those among the background population to provide estimates of differences in risk (excess risk). If detection of VZV DNA in the CSF is causally linked to dementia, possible mechanisms behind such associations could be cerebral damage caused by the virus itself or the vasculopathy that may complicate VZV infection. [35] Detection of VZV DNA in the CSF was also associated with an increased risk of new onset epilepsy, which is in accordance with the increased risk of epilepsy following CNS infections in general. [36] We add to previous studies by demonstrating that the use of antiepileptic medicine was substantially and persistently increased following detection of VZV DNA in the CSF, indicating that epilepsy and seizures might permanently complicate detection of VZV DNA in the CSF. We also demonstrated that more patients in the VZV cohort than individuals in the comparison cohort had epilepsy and used antiepileptics *before* study inclusion. This association might reflect that patients with epilepsy often have lumbar puncture performed following seizures. [37] If so, oligo- or even asymptomatic VZV positivity [10] in the spinal fluid would be detected more frequently among these patients.

We did not demonstrate any increased risk of psychiatric disease, including mood affective disorders. Despite this, redemption of antidepressants increased following detection of VZV DNA in

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the CSF. There are several potential explanations for this finding. As the risk of herpes zoster is increased among patients with depression, [38,39] the increased redemption of antidepressant following detection of VZV DNA in the CSF might be caused by a worsening of preexisting depression to levels that necessitate pharmaceutical intervention. Also, the increased use of antidepressant following detection of VZV DNA in the CSF might be explained by the role for antidepressant in the management of neuropathic pain in postherpetic neuralgia. [40] A similar explanation was recently suggested for the association between the use of antidepressant and Lyme neuroborreliosis. [17] Further investigation of the potential association between detection of VZV DNA in the CSF and depression is warranted. We also noted an increased use of medicine used for the nervous system *before* study inclusion among patients in the VZV cohort. This could indicate that patients in the VZV cohort constitute a fragile population, a point that needs to be considered before making causal inference whether VZV causes psychiatric disease.

Although we had insufficient power to conclude whether detection of VZV DNA in the CSF is associated with a deterioration in social functioning, it seemed that income decreased, and disability pension reception and nursing home residency increased following detection of VZV DNA in the CSF. This corroborates findings from previous studies of VZV encephalitis in which approximately half of the patients had an unfavorable outcome, defined as a Glasgow Outcome Score of 4 or lower [32,33].

Conclusion

Our study demonstrates that immunosuppression and comorbidity is associated with an increased risk of detection of VZV DNA in the CSF and that detection of VZV DNA in the CSF is associated with an increased risk of death, compared with the background population. Even patients without immunosuppression and comorbidity have an increased mortality, but to a much lower extent than the overall patient group. Finally, detection of VZV DNA in the CSF is associated with neurologic sequelae and an increased use of antiepileptics and antidepressants.

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Declaration of interests

All authors declare no competing interests.

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Table 1. Characteristics of the study cohorts.

	VZV cohort N = 517	Comparison cohort N = 9823
Age, median (IQR)	59 (31 to 77)	59 (31 to 77)
Age 15 years or more, n (%)	463 (90)	8797 (90)
Male, n (%)	249 (48)	747 (48)
VZV-DNA-CSF category		
Encephalitis, n (%)	227 (44)	N.A.
Meningitis, n (%)	109 (21)	N.A.
Herpes zoster, n (%)	74 (14)	N.A.
Other, n (%)	107 (21)	N.A.
Comorbidity*, n (%)	266 (51)	2957 (30)
Immunosuppressive condition, n (%)	131 (25)	1271 (13)
Transplantation (solid/hematopoietic), n (%)	18 (3)	19 (0)
HIV, n (%)	12 (2)	2 (0)
Cancer, (%)	56 (11)	687 (7)
Inflammatory bowel disease, n (%)	10 (2)	92 (1)
Systemic lupus erythematosus, n (%)	2 (0)	10 (0)
COPD, n (%)	40 (8)	418 (4)
Rheumatoid arthritis, n (%)	11 (2)	109 (1)
Ankylosing spondylitis, n (%)	1 (0)	14 (0)
Psoriasis, n (%)	8 (2)	63 (1)
Neurologic disease		
Dementia, n (%)	17 (3)	156 (2)
Epilepsy, n (%)	26 (5)	142 (1)
Psychiatric disease overall, n (%)	27 (5)	459 (5)

Abbreviations: IQR, interquartile range; N.A., Not applicable; VZV, varicella zoster virus; DNA, Deoxyribonucleic acid; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; COPD, chronic obstructive pulmonary disease. * : Comorbidity was defined as a Charlson Comorbidity Index score of 1 or more.

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Table 2. Proportion of patients in the VZV cohort and of individuals in the comparison cohort with prior hospitalization, immunosuppressive medicine, comorbidity and immunosuppressive conditions, as well as odds ratios (ORs) of these factors for detection of VZV DNA in the cerebrospinal fluid.

Years from study inclusion	VZV cohort	Comparison cohort	Difference (95% CI)	OR (95% CI)
		Proportion hospitalized (%)		
- 5	20	14	6 (3 to 10)	1.6 (1.3 to 2.1)
- 2	29	15	14 (10 to 18)	2.5 (2.0 to 3.1)
- 1	30	15	14 (10 to 18)	2.5 (2.0 to 3.0)
		Proportion treated with immunosuppressive medicine (%)		
- 5	14	4	9 (6 to 12)	3.5 (2.6 to 4.6)
- 2	17	5	12 (9 to 15)	4.1 (3.2 to 5.3)
- 1	18	5	13 (10 to 17)	4.3 (3.4 to 5.6)
		Proportion with comorbidity *(%)		
- 5	33	21	12 (8 to 16)	2.0 (1.6 to 2.5)
- 2	42	27	16 (11 to 20)	2.4 (1.9 to 3.0)
- 1	45	29	16 (11 to 20)	2.4 (2.0 to 3.0)
		Proportion with immunosuppressive conditions (%)		
- 5	11	6	6 (3 to 9)	2.2 (1.6 to 3.0)
- 2	18	9	10 (6 to 13)	2.5 (2.0 to 3.3)
- 1	21	10	11 (8 to 15)	2.6 (2.1 to 3.4)

Abbreviations: VZV, varicella zoster virus; OR, odds ratio. * : Comorbidity was defined as a Charlson Comorbidity Index score of 1 or more.

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Table 3. Mortality and neurologic morbidity among patients in the VZV cohort and individuals in the comparison cohort, stratified according to patient category.

		1y				12 y			
Patient category	Outcome	1-year risk - VZV cohort (%)	1-year risk - comparison cohort (%)	Difference in 1-year risk (95% CI) (%)	Relative risk for the period 0-1 years after study inclusion (95% CI)	12 year risk- VZV cohort (%)	12 year risk - comparison cohort (%)	Difference in 12 years risk (95% CI) (%)	Relative risk for the period 1-12 years after study inclusion (95% CI)
All	Mortality	12	3	9 (6 to 12)	5.65 (4.24 to 7.53)	42	31	11 (4 to 18)	1.54 (1.21 to 1.95)
	Neurologic morbidity								
	Dementia	1.5	0.6	0.9 (-0.2 to 1.9)	3.41 (1.52 to 7.67)	7.7	4.9	2.7 (-0.7 to 6.1)	2.42 (1.43 to 4.08)
	Epilepsy	1.5	0.1	1.3 (0.2 to 2.4)	15.04 (6.23 to 36.30)	5.1	1.1	4.0 (1.2 to 6.9)	5.45 (2.57 to 11.56)
	Psychiatric disease	0.6	0.3	0.3 (-0.4 to 1.0)	2.2 (0.7 to 7.3)	3.8	4.0	-0.3 (-2.8 to 2.3)	1.0 (0.5 to 2.1)
No immunosuppression/comorbidity[§,α,£]	Mortality	2	0	2 (-1 to 4)	N.A.*	17	11	6 (-5 to 16)	1.49 (0.67 to 3.33)
Aged 15 years or more[§]	Mortality	13	3	10 (6 to 13)	5.37 (4.01 to 7.20)	46	35	11 (3 to 19)	1.52 (1.19 to 1.93)
	Neurologic morbidity								
	Dementia	1.6	0.7	1.0 (-0.3 to 2.2)	3.41 (1.52 to 7.67)	8.5	5.5	3.0 (-0.8 to 6.8)	2.42 (1.43 to 4.08)
	Epilepsy	1.2	0.2	1.0 (0.0 to 2.0)	8.28 (2.88 to 23.85)	4.6	1.0	3.6 (0.6 to 6.6)	5.27 (2.25 to 12.35)
Encephalitis[&]	Mortality – all patients	12	4	8 (4 to 8)	3.7 (2.4 to 5.7)	55	38	17 (6 to 29)	1.6 (1.2 to 2.2)
	Neurologic morbidity								
	Dementia	1.9	0.6	1.3 (-0.6 to 3.1)	3.6 (1.2 to 10.7)	12.4	6.2	6.2 (0.0 to 12.3)	3.6 (2.0 to 6.6)
	Epilepsy	1.9	0.1	1.8 (-0.1 to 3.6)	18.4 (4.6 to 73.5)	4.1	0.8	3.3 (0.1 to 6.4)	4.5 (1.3 to 16.3)
Meningitis[¤,&]	Mortality – all patients	5	1	3 (-1 to 7)	4.9 (1.8 to 13.0)	20	16	4 (-10 to 18)	0.9 (0.4 to 2.1)
	Neurologic morbidity								
	Dementia	0.0	0.3	-0.3 (-0.5 to -0.1)	N.A.	3.7	3.0	0.7 (-6.7 to 8.1)	1.5 (0.2 to 13.1)
	Epilepsy	0.9	0.1	0.9 (-1.0 to 2.7)	19.0 (1.2 to 303.8)	0.9	1.0	-0.1 (-2.2 to 2.0)	N.A.
Herpes zoster[#,&]	Mortality – all patients	10	3	6 (0 to 13)	4.2 (1.8 to 9.5)	42	40	2 (-15 to 19)	2.1 (1.2 to 3.6)
	Neurologic morbidity								
	Dementia	4.7	1.1	3.6 (-1.6 to 8.9)	7.4 (1.9 to 28.7)	6.9	5.7	1.2 (-5.7 to 8.1)	1.2 (0.2 to 9.3)
	Epilepsy	0.0	0.3	-0.3 (-0.6 to 0.0)	N.A.	5.2	1.5	3.8 (-3.5 to 11.1)	6.6 (1.3 to 34.0)
Other[$,&]	Mortality – all patients	22	2	20 (12 to 28)	20.5 (11.3 to 37.0)	34	27	7 (-4 to 18)	1.2 (0.6 to 2.4)
	Neurologic morbidity								
	Dementia	0.0	0.6	-0.6 (-1.0 to -0.3)	N.A.	1.4	4.1	-2.7 (-5.7 to 0.4)	0.6 (0.1 to 4.5)
	Epilepsy	2.1	0.2	1.9 (-1.0 to 4.8)	17.5 (2.5 to 124.1)	9.7	1.3	8.4 (-0.2 to 17.0)	8.9 (2.7 to 29.7)

[§]: Applies for both patient in the VZV cohort and individuals in the comparison. Matching ratio in these analyses were (1:3). [&]: Stratified according to the patient category of the detection of VZV DNA in the CSF patient. *: Not applicable due to too few events among either patients in the VZV cohort or among individuals in the comparison cohort. [¤]: Meningitis, and no encephalitis, [#]: Herpes zoster, and no encephalitis or meningitis, [$]: Other, which means no encephalitis, meningitis or herpes zoster. [£]: Comorbidity was defined as a Charlson Comorbidity Index score of 1 or more.

Abbreviations: VZV, varicella zoster virus, CI, confidence interval; N.A., Not applicable.

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FIGURES

FIGURE LEGENDS

Figure 1. Admission (A), immunosuppressive medicine (B), comorbidity according to Charlson Comorbidity Index (C) and immunosuppressive conditions [HIV, inflammatory bowel disease, systemic lupus erythematosus, chronic obstructive pulmonary disease, rheumatoid arthritis, ankylosing spondylitis and psoriasis] (D) among patients in the VZV cohort and individuals in the comparison cohort from 5 years before study inclusion to 5 years after study inclusion.

Figure 2. Survival and neurologic and psychiatric morbidity among patients in the VZV cohort and individuals in the comparison cohort. Survival (A), dementia (B), epilepsy (C) and psychiatric disease overall (D).

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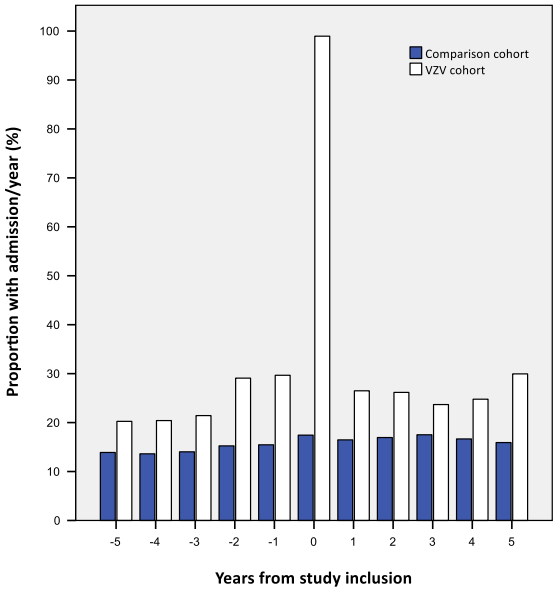
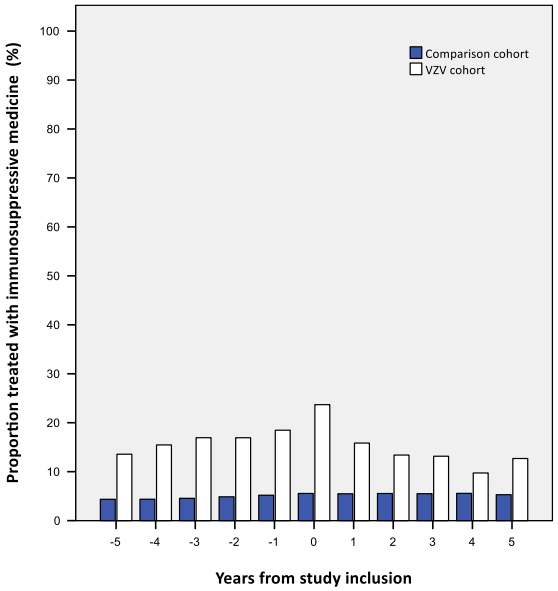
FIGURE 1

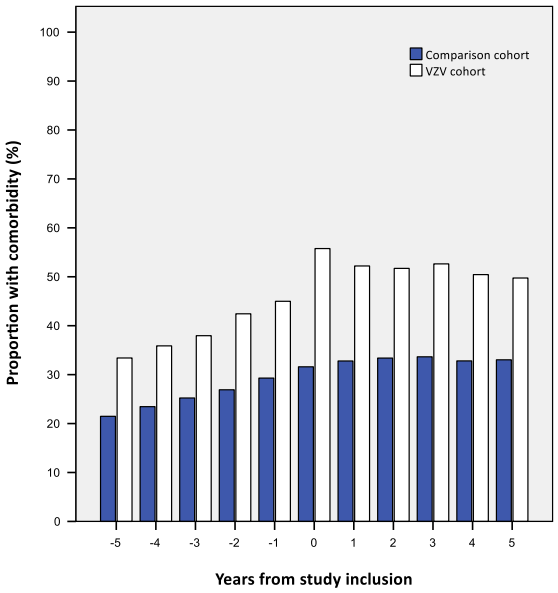
A)



B)



C)



D)

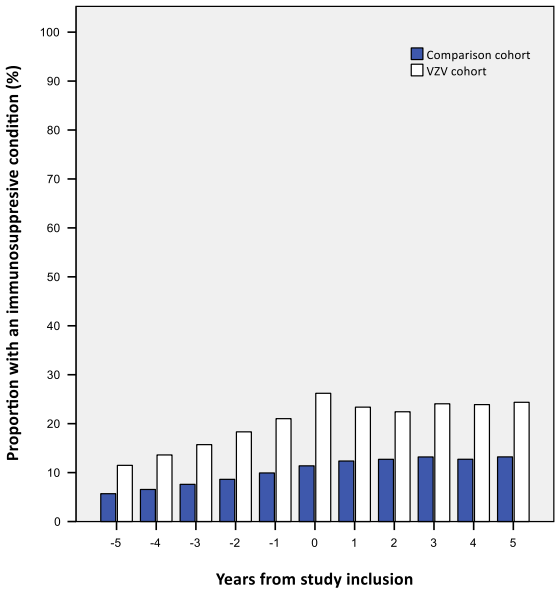


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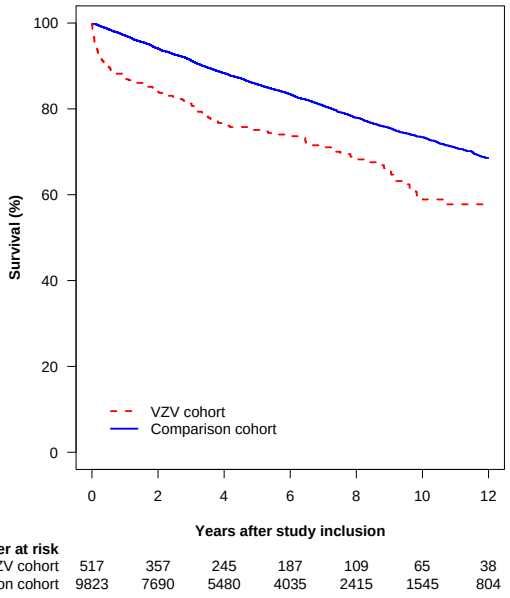
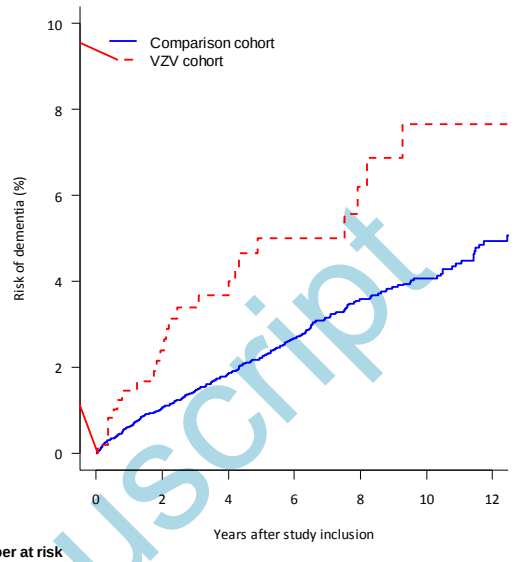
FIGURE 2

A



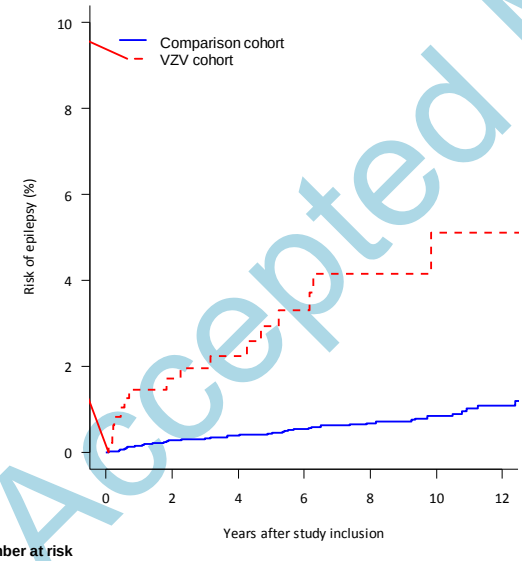
Number at risk							
VZV cohort	517	357	245	187	109	65	38
Comparison cohort	9823	7690	5480	4035	2415	1545	804

B



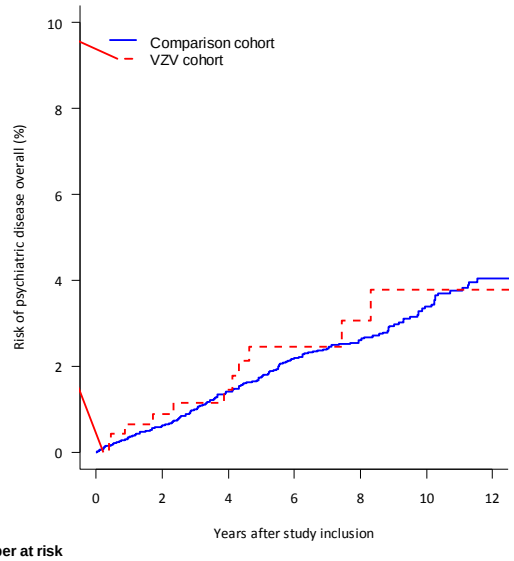
Number at risk							
VZV cohort	500	341	238	180	104	63	37
Comparison cohort	9667	7552	5391	3968	2368	1514	787

C



Number at risk							
VZV cohort	491	342	234	178	103	59	34
Comparison cohort	9681	7573	5401	3974	2378	1517	790

D



Number at risk							
VZV cohort	490	336	231	174	97	58	35
Comparison cohort	9364	7338	5219	3815	2270	1445	750

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