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Varicella Zoster Virus encephalitis in Denmark from 2015 to 2019 - A nationwide prospective cohort study

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Key words: Encephalitis, viral encephalitis, varicella zoster virus, vasculitis.

Key points: We identified 92 adults with VZV encephalitis primarily affecting elderly or immuno-compromised patients. Diagnosis and treatment are often delayed and cerebral vasculitis not uncommon (16%). Risk factors for unfavorable outcome are age, cerebral vasculitis, and Glasgow coma scale score <15.

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Abstract

Background: Knowledge of the epidemiology and clinical characteristics of Varicella zoster virus (VZV) encephalitis remains limited.

Methods: Nationwide prospective cohort study of adults treated for microbiologically confirmed VZV encephalitis at Danish departments of infectious diseases from 2015 to 2019. Modified Poisson regression analysis was used to compute adjusted relative risks (RR) of unfavorable outcome.

Results: We identified 92 adults (49% female) with VZV encephalitis yielding an incidence of 5.3/1,000,000/year (95% CI:4.2-6.6). The median age was 75 years (IQR 67-83) and immuno-compromising conditions were frequent (39%). Predominant symptoms were confusion (76%), headache (56%), nausea (45%), gait disturbance (42%), and personality changes (41%). Cranial imaging showed cerebral vasculitis (including infarction and hemorrhage) in 14 (16%) patients and encephalitic abnormalities in 11 (13%) with predilection for the brainstem and deep brain structures. Intravenous acyclovir treatment was initiated a median of 13.4 hours (IQR 5.2-46.3) since admission, while cranial imaging and lumbar puncture were performed after 6.3 hours (IQR 2.5-31.0) and 18.5 hours (IQR 4.9-42.0). In-hospital, 1-month, and 3-month mortalities were 4%, 9%, and 11%, respectively. Unfavorable outcome (Glasgow Outcome Score (GOS) of 1-4), was found in 69% at discharge, with age (adj. RR 1.02, 95% CI 1.01-1.03), vasculitis (adj. RR 1.38, 95% CI 1.02-1.86), and Glascow coma scale (GCS)<15 (adj. RR 1.32, 95% CI:1.01-1.73) identified as independent risk factors.

Conclusion: VZV encephalitis occurs primarily in elderly or immuno-compromised patients with a higher incidence than previously estimated. The diagnosis is often delayed and risk factors for unfavorable outcome are age, cerebral vasculitis, and GCS<15.

Introduction

Varicella zoster virus (VZV) is a frequent cause of sporadic viral encephalitis in the Western world and is associated with a mortality of 9-20% [1–3]. Incidence of VZV encephalitis has been estimated to be ~2-4/1,000,000/year similar to that of herpes simplex virus encephalitis (HSE) [4–6]. Primary infection with VZV presents as varicella (chickenpox), after which the virus establishes long-lasting latency in sensory cranial neurons or dorsal root ganglia [7]. Approximately 90 % of the adult world population is infected with VZV [8]. Reactivation of VZV can result in various clinical manifestations, of which the most frequent is herpes zoster. Rarely, however, infected individuals may develop severe neurological complications, such as meningitis, encephalitis, cerebellitis or central nervous system (CNS) vasculitis. Risk factors for VZV encephalitis include age >50 years and immuno-compromising conditions such as AIDS, organ transplantation, cancer, or immune-modulating therapy [9]. Moreover, a number of rare primary immunodeficiencies have also been associated with VZV encephalitis [10–12].

The routine virologic analysis for VZV encephalitis is PCR analysis of cerebrospinal fluid (CSF)[2,13]. In addition, VZV CNS infection may be detected in the CSF by measuring intrathecal anti-VZV IgG, which may sometimes be positive late during infection and or in VZV vasculitis, where PCR may not always be positive [14]. Finally, brain magnetic resonance imaging (MRI) may show encephalitic changes, although there is no typical presentation and scans are often normal [15].

Previous studies of VZV encephalitis in adults are scarce and characterized by limited sample size [2,3,5] or restricted to laboratory surveillance without detailed clinical information [4]. Thus, further contemporary studies are essential in order to improve diagnosis and treatment. We used a nationwide prospective database on CNS infections to

investigate the epidemiology, clinical characteristics, diagnostics, and outcome in adults with VZV encephalitis in Denmark from 2015 to 2019.

Methods

Setting and study population

We accessed the database of the Danish Study Group of Infections of the Brain (DASGIB) to identify all adults (≥18 years of age) treated for first-time VZV encephalitis at departments of infectious diseases (ID) in Denmark from 1st of January 2015 to 30th of September 2019 (Figure 1). DASGIB is a nationwide collaboration between all Danish departments of ID prospectively registering all patients with central nervous system (CNS) infections [16].

Only patients with a confirmed microbiological diagnosis of VZV CNS infection (by positive PCR or intrathecal antibody ratio) were included. The diagnosis of VZV encephalitis was established by an infectious diseases specialist at each center according to criteria defined by the International Encephalitis Consortium (IEC) [17] or an altered mental status (*i.e.* impaired consciousness, lethargy, or personality changes) combined with other symptoms of encephalitis (*e.g.* fever or a focal neurological deficit). Cases of proven or suspected autoimmune encephalitis were excluded. Patient enrollment was evaluated by ad hoc case-to-case discussions at biannual study group meetings. Furthermore, database completeness was ensured through annual searches of International Classification of Diseases 10th revision codes (A88, B01.1, B02.1, G05) in local databases of all eight ID departments in Denmark.

The entire Danish population has unrestricted access to tax-financed medical care. In accordance with recommendations of the Danish health authorities, all patients with CNS infections in Denmark are treated at specialized departments of ID. The adult (≥18 years of

age) population of Denmark was ~4.5 million in 2015 (Statistics Denmark, https://www.statbank.dk/).

Clinical data

Baseline characteristics including demographics, time and place of admission, exposures, co-morbidities, as well as clinical signs and symptoms at admission were prospectively collected in the database. During hospitalization we registered antiviral treatment, cranial imaging and laboratory results from the diagnostic workup. Timing of lumbar puncture and cranial imaging was extracted from electronic records at departments of biochemistry or radiology, respectively. Timing of antiviral therapy was identified in the electronic medication systems. Time to lumbar puncture, cranial imaging, and onset of antiviral therapy was computed as time from admission to each of the above events.

Outcome was categorized according to the Glasgow Outcome Scale (GOS): 1. Death; 2. Vegetative state; 3. Severe sequelae and dependency upon others in daily life; 4. Moderate sequelae but with the ability to live independently; and 5. No or only mild sequelae [18]. Outcome was assessed at discharge and at outpatient visits one and three months after discharge. A GOS score of ≤4 was considered an unfavorable outcome.

Statistical analyses

To describe baseline demographics, we used frequency distributions. Continuous non-parametric data were summarized using medians, interquartile ranges (IQR), and ranges. The 95% confidence intervals (CI) were estimated assuming binomial proportions. Categorical variables were compared by Chi squared test and continuous variables by Mann-Whitney U-test. A two-tailed significance level was set at $P < 0.05$.

The incidence rate (IR) was calculated as the number of incident cases per million at risk based on quarterly population data in Denmark from 2016-2019 (first quarter) (Statistics Denmark, https://www.statbank.dk/).

We used modified Poisson regression analysis [19] to compute relative risks (RR) with 95% CIs for unfavorable outcome at discharge adjusted for age, sex, cerebral vasculitis, time to IV acyclovir treatment (0-24 h, 24-48 h, and >48 h), GCS <15, and adjunctive dexamethasone treatment.

All statistical analyses were performed with Stata Software (v. 13.1; Stata Corp. College Station, TX).

Ethics

The DASGIB cohort study was approved by The Danish Data Protection Agency (record no. 2012-58-0018) and The Danish Board of Health (record no. 3-3013-2579/1 and 3-3013-3168/1). The study has been reported according to STROBE guidelines.

Results

During the study period, we identified 92 (26%) adults with VZV encephalitis out of 353 patients with encephalitis in the DASGIB database (Figure 1). We estimated an IR of 5.3/1,000,000/year (95% CI 4.2-6.6).

Patient characteristics

All patients fulfilled the IEC major criterion of an altered mental status lasting ≥24 h at admission (87/92) or later during hospitalization (5/92), and 71/92 (77%) had confirmed encephalitis according to the IEC criteria. The remaining patients had an altered mental status combined with either CSF leukocytes >5/mL (n=15), temperature ≥38°C (n=2), EEG

suggestive of encephalitis (n=1), or were included due to hallucinations and personality changes combined with cutaneous zoster (n=3). Patients with VZV encephalitis had a median age of 75 years (IQR: 67-83) and 45/92 (49%) were female (Table 1). The majority of patients (52%) had no previous physical or cognitive deficits before admission. Immuno-compromising conditions were present in 36/92 (39%) patients including immune-suppressive treatments such as prednisolone or other drugs (18), diabetes mellitus (11), solid or hematological cancer (10), and alcohol abuse (5). No patients had a known primary immunodeficiency.

The median duration of symptoms before admission was 4 days (IQR: 2-7) and most patients presented with confusion (76%), headache (56%), nausea (45%), or a previous history of herpes zoster (70%). Other frequent clinical manifestations included gait disturbances (42%), personality changes (41%), and aphasia (21%). Notably, 38% of patients had a GCS <15. Only eight (9%) and seven (8%) patients had a GCS ≤12 and ≤10. Median temperature at admission was 37.5°C (IQR: 36.8-38.3). We found no differences in the clinical presentation of VZV encephalitis with or without cutaneous herpes zoster besides rash. A tentative diagnosis of encephalitis was made in nine patients (11%) at admission, while the presence of herpes zoster was noted in another nine (11%). Other admission diagnoses were heterogeneous ranging from non-infectious neurological disorders (21%) to cerebrovascular disease (15%).

Diagnostic workup

Patients with VZV encephalitis had a median C-reactive protein of 6 mg/L (IQR: 3-23) and a median white blood cell (WBC) count of 7.7×10^9/L (IQR: 6.1-9.1) (Table 2). Median time from admission to lumbar puncture was 18.5h (IQR: 4.9-42.0) and 82/91 (90%) had CSF

pleocytosis (median WBC of 146×10^9 cells/L [IQR; 50-286]) with a mononuclear predominance. VZV in the CSF was detected by PCR in 86/92 (93%) and by a positive intrathecal VZV-IgG index in 6/92 (7%). Among patients diagnosed by intrathecal VZV-IgG index, two patients had delayed lumbar puncture (>5 days after admission) and none had vasculitis. Of eight patients examined for autoimmune encephalitis antibodies (blood/CSF) analysis, none tested positive.

Cranial imaging was performed in 85/92 patients (92%, Table 3) with a median time from admission to first scan (CT or MRI) of 6.3h (IQR: 2.5-31). The most frequent pathologies included signs of vasculitis including infarction/hemorrhage (16%) and encephalitic changes (13%). We observed a clear predilection of abnormalities for the brainstem, deep brain structures including the basal ganglia, and the cerebellum. Vasculitis was detected a median seven days upon start of admission (IQR: 4-10). Notably, most patients did not show any radiological signs of intracranial pathology excluding age-related findings (*e.g.* leukoaraiosis/atrophy). Electroencephalography suggested encephalitis in 24/46 (52%).

Treatment and outcome

All patients were treated with intravenous (IV) acyclovir 10 mg/kg t.i.d. with a median time from admission to acyclovir administration of 13.4h (IQR: 5.2-46.3) (Table 4). In addition, 23/89 (26%) were initially treated with short courses of adjunctive dexamethasone (<96h) due to suspected bacterial meningitis until VZV encephalitis was confirmed. Vasculitis patients received longer courses of glucocorticoid. The median duration of IV acyclovir was 14 days (IQR: 7-14) followed by oral acyclovir in 43/90 (48%) for a median of 11 days (IQR: 7-15). Admission to the intensive care unit occurred in 13/92 (14%) of patients.

We observed in-hospital, 1- and 3-months mortality rates of 4/92 (4%), 8/92 (9%) and 10/92 (11%), respectively, with all fatalities restricted to patients ≥75 years of age. Causes of death during admission were aspiration pneumonia and pontine hemorrhage. Unfavorable outcome (GOS<5) at one and three months after discharge occurred in 46/83 (55%) and 41/80 (51%) of patients. The presence of pre-existing physical or cognitive deficits were significantly associated with unfavorable outcome and 1-month mortality. Using modified Poisson regression, we identified age (adj. RR 1.02, 95% CI: 1.01-1.03), vasculitis (adj. RR 1.38, 95% CI: 1.02-1.86), and GCS<15 (adj. RR 1.32, 95% CI: 1.01-1.73) as independent risk factors for unfavorable outcome in VZV encephalitis in adjusted analyses. Due to few observations, GCS ≤12 and ≤10 were omitted from the adjusted analysis.

Discussion

The epidemiology, clinical characteristics and outcome of VZV encephalitis remain poorly described. In this prospective nationwide cohort study, we investigated the epidemiology and clinical presentation of VZV encephalitis in adult patients in Denmark considering incidence, clinical manifestations, diagnostic workup, time to treatment, and outcome. Our main findings included a higher incidence of VZV encephalitis than previously reported both in terms of general population incidence (5.3/1,000,000/year) [4,5] and proportion among encephalitis patients (26%) compared with other studies outside of Northern Europe [2,3,20]. The majority of patients were elderly and more than one third were immunocompromised. Signs of cerebral vasculitis were present in 16% and were detected a median seven days after time of admission. VZV vasculitis is most probably underdiagnosed with few patients having MRI angiography done, and vasculitis was independently associated with unfavorable outcome. Age and GCS<15 on admission were also associated with poor outcome. Finally, we

identified significant delays in diagnosis and antiviral treatment initiation, which may have clinical implications.

We estimated an IR in adults of 5.3/1,000,000/year, suggesting that VZV encephalitis and infectious encephalitis in general may be underreported [21]. The clinical phenotype of viral CNS infections often varies greatly ranging from relatively benign meningitis to severe encephalitis with neurological sequelae [1,22]. Thus, the differentiation between viral meningitis, meningoencephalitis, and encephalitis can be challenging, which could imply an overestimation of the IR. However, we applied the IEC major diagnostic criteria (altered mental status) combined with detection of VZV in the CSF of all patients to ensure strict enrollment and minimize this bias[17]. On the other hand, strict inclusion requiring a lumbar puncture could result in cases of VZV (meningo)encephalitis not being properly examined and referred to ID departments as required for inclusion in the cohort. Likewise, a few patients with VZV encephalitis occurring during chemotherapy/immunomodulatory treatment admitted at other medical departments may have occurred.

The fraction of immunocompromised versus immunocompetent individuals acquiring VZV encephalitis remains unknown. Historically, VZV CNS infections have been described to mostly affect immunocompromised patients [9]. As VZV is increasingly recognized as a cause of CNS infection [1], the question remaining is whether VZV encephalitis should continue to be considered as a disease mostly restricted to immunocompromised patients. In our cohort, 39% of the patients were classified as immunocompromised, and many patients were elderly and subject to immunosenescence. This may imply future increases in VZV encephalitis given the increasing number of immunocompromised individuals and changing demographics towards a larger proportion of elderly persons. Still, the majority of patients in this study were not immunocompromised

We made several interesting observations requiring further elaboration. A high positive rate was encountered for the detection of VZV by PCR in CSF (86/92, 93%) which confirms this method as first choice. In contrast, only 6 (7%) individuals were diagnosed by intrathecal anti-VZV IgG titer suggesting that this analysis should be reserved for cases of putative false negatives from PCR analyses with a persistent clinical suspicion of VZV CNS infection. Radiological examinations showed that 14 (16%) patients had findings of cerebral vasculitis, thus constituting the most common intracranial pathology in our cohort followed by encephalitic changes in 11 (13%). Consistent with previous studies on VZV encephalitis, these radiological abnormalities were common in the brainstem, deep brain structures, and cerebellum [9,20,22,23]. Notably, we identified vasculitis as a risk factor for unfavorable outcome and this group of patients warrants further investigation.

Adjunctive treatment of VZV encephalitis remains incompletely determined, particularly the question relating to the effect of glucocorticoids in limiting neuroinflammation. In herpes simplex encephalitis patients, adjunctive therapy with glucocorticoids has been reported an independent predictor of improved outcome [24], but robust evidence to support this clinical practice is still lacking [25]. Although 26% of the patients in the present study had received treatment with dexamethasone, we failed to find any significant associations to any outcome measures. This analysis is also likely to be confounded by indication, *e.g*. patients with more critical disease more likely to receive dexamethasone. Most authorities in the field agree that administration of glucocorticoids should be considered in the treatment of VZV vasculitis [26]. Yet, a randomized controlled trial of glucocorticoids in VZV encephalitis is required to definitively answer this question.

An important finding of our study was that many patients were not suspected of VZV encephalitis at admission and the associated median delay in antiviral treatment of 13.4h

after admission[27]. This could potentially aggravate the prognosis, however, we were unable to confirm this in our study. Focus on the importance the diverse clinical presentation of viral encephalitis and early administration of acyclovir should be emphasized.

In this cohort we found an unfavorable outcome (GOS <5) one month after discharge in 55% of the patients, which is higher than previously reported [3]. Ten (11%) patients died following the diagnosis of VZV encephalitis during admission until 3 months after discharge, all aged ≥75 years, and age was confirmed as an independent risk factor for unfavorable outcome together with presence of vasculitis and GCS<15 at admission. Knowledge on neurological sequelae of VZV encephalitis is still scarce and predominantly based on small descriptive case series [22,28,29]. Larger studies addressing the outcome of encephalitis in general do exist, though only with limited number of VZV patients. In one of these studies the mortality and risk of neurological sequelae in VZV encephalitis was equal to that of HSE [2,30]. The neurological sequelae varied from minor to severe and was mainly described as neuropsychological including impaired concentration and memory, slowing of cognitive processing and behavioral changes [22,28–30]. Unfortunately, limitations on detailed information regarding sequelae following discharge precluded further analyses of this in our cohort.

The nationwide and population-based setting of this cohort study including patients from all ID departments in Denmark constitutes the key strengths of this study. Continuous data registration in a pre-defined registration form helped preventing potential recall bias or misclassification and allowed us to collect data independently of future events, such as death. Additionally, the use of DNA-based diagnostic technologies did not change during the four years of inclusion. Still, some limitations have to be considered when interpreting our results.

Minor incidents of viral CNS infection could potentially be encountered at other medical departments in Denmark without reporting to DASGIB. However, according to the Danish Health Authorities all patients with CNS infections are to be treated by ID departments in Denmark and thus, we find this unlikely. Second, despite the prospective design of the study, data completeness for some variables varied. Some patients were transferred to the ID department late in their disease course, which may have caused limitations in data availability. Standardized outcome measurements in encephalitis are lacking and although GOS is frequently used in studies of CNS infections, it may have limited sensitivity in differentiating patients with moderate or minor sequelae ('ceiling effect') compared with the extended GOS score [31] Finally, the clinical follow-up of up to three months was not complete for all patients and some may experience further improvement for up to one year after infection.

In conclusion, the incidence of VZV encephalitis among adults in Denmark is higher than previously reported and immuno-compromise is a frequent predisposing condition. Diagnosis remains difficult and treatment is often delayed. Radiological abnormalities included vasculitis and encephalitic lesions with predilection for brainstem, basal ganglia and cerebellum. We identified age, vasculitis and GCS<15 as independent risk factors for unfavorable outcome. Large prospective studies and randomized controlled trials are needed to increase knowledge on disease pathogenesis and prognostic factors in order to improve diagnosis and treatment of patients with VZV infection in the CNS.

Members of the Danish Study Group for Infections in the Brain (DASGIB):

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Conflicts of interest

The authors have no conflicts of interest to declare.

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Author contributions

LKH, KSH, JB and THM conceived the study and wrote the first draft. LKH and JB performed the statistical analyses. JB and HN organized and managed the DASGIB cohort. KSH, JB, LL, CB, CØA, BRH, HRL, JHL, LW, MS, HN, and THM collected data and participated in critical review of the manuscript.

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Tables

Table 1. Baseline characteristics at admission of 92 adult VZV encephalitis patients in Denmark from 2015-2019.

Variable	Obs	*N* (%) / median (IQR)
Age, years	92	75 (67-83)
Sex, female	92	45 (49)
Comorbidity / immunosuppression	92	36 (39)
Alcohol abuse		5 (5)
Organ transplant		0
Solid cancer		8 (9)
Hematological cancer		2 (2)
Diabetes mellitus		11 (12)
HIV		1 (1)
Prednisolone (any dosage)		8 (9)
Other immuno-suppressants*		10 (11)
Known primary immunodeficiency		0
No physical or cognitive deficits before admission	88	46 (52)
History of herpes zoster at any time before admission	83	58 (70)
Duration of symptoms, days	91	4 (2-7)
Clinical presentation		
Confusion	90	68 (76)
Headache	80	45 (56)
Nausea	80	36 (45)
Gait disturbance	74	31 (42)
Personality changes	86	35 (41)
Level of consciousness		
GCS 15	91	56 (62)
GCS 13-14	91	27 (30)
GCS 10-12	91	3 (3)
GCS <10	91	5 (5)
Median GCS at admission	91	15 (14-15)
Fever (≥38.0°C)	91	34 (37)
Median temp. at admission (°C)	91	37.5 (36.8-38.3)
Aphasia	82	17 (21)
Extremity motor/sensory deficits	83	16 (19)
Cranial nerve palsy	88	15 (17)
Seizures (preceding or at admission)	87	10 (11)
Ataxia	74	7 (9)
Diagnosis at admission	80	
Non-infectious neurological disease		17 (21)
Cerebrovascular disease**		12 (15)
Non-CNS infection		11 (14)
Encephalitis		9 (11)
Herpes zoster		9 (11)
Psychiatric disease		1 (1)
Miscellaneous		21 (26)

*Methotrexate, n=6; TNF-alpha inhibitor, n=1; azathioprin, n=1. **Includes stroke, cranial hemorrhages, and syncope; GCS, Glascow coma scale.

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Table 2. Biochemical and microbiological analyses of 92 adult VZV encephalitis patients in Denmark from 2015-2019.

Variable	Obs	*N* (%) / median (IQR; range)	Reference range
Blood analysis			
C-reactive protein (mg/L)	88	6 (3-23)	<3
WBC count ($\times 10^9$/L)	92	7.7 (6.1-9.3)	3.5-10
Platelet count ($\times 10^9$/L)	88	217 (163-267)	145-350
Creatinine (μM)	90	82 (66-105)	60-105
Cerebrospinal fluid analysis			
Time to lumbar puncture (h)*	92	18.5 (4.9-42.0)	
WBC count ($\times 10^6$/L)	91	146 (50-286; 1-1413)	<5
PMN cells ($\times 10^6$/L)	81	3 (1-7; 0-98)	0
Protein (g/L)	88	0.92 (0.7-1.5; 0.2-10.1)	0.15-0.85
Erythrocytes ($\times 10^6$/L)	83	4 (0-300; 0-11,000	<300
CSF glucose (mM)	91	3.5 (3.0-4.3; 1.6-8.3)	2.5-4.5
Lactate (mM)	33	2.6 (2.1-4.3; 0.5-9.0)	0.9-2.8
CSF bacterial culture, positive	72	0 (0)	
Autoimmune encephalitis antibodies**, positive	8	0 (0)	
VZV encephalitis diagnosed by			
PCR in CSF	92	86 (93)	
Intrathecal VZV-IgG index	36	6 (7)	

CSF: Cerebrospinal fluid. CT: Computed tomography. EEG: Electroencephalography. MRI: Magnetic resonance imaging. PMN: Polymorphonuclear. WBC: White blood cell count.
*From time of admission. ** CSF in four patients, blood in one patient, and both CSF and blood in another three patients..

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Table 3. Results of cranial imaging and EEG in 92 adult VZV encephalitis patients in Denmark from 2015-2019.

Variable	Obs	***N* (%)** / median (IQR)
Cranial imaging (any) during admission	92	85 (92)
Cranial CT scan		72 (78)
Cranial MRI		66 (72)
Both CT and MRI		53 (48)
Time to cranial imaging (from time of admission)		
Time to CT scan (h)	71	4.7 (2.2-26.2)
Time to MRI scan (h)	66	71.3 (47.2-144)
Time to first cranial scan (h)	85	6.3 (2.5-31.0)
Imaging findings	85	
Vasculitis incl. brain infarction and hemorrhage*		14 (16)
Frontal lobe		3
Parietal lobe		4
Temporal lobe		1
Occipital lobe		2
Cerebellum		1
Brainstem		3
Other deep structures incl. basal ganglia		3
Encephalitic abnormalities*		11 (13)
Frontal lobe		1
Parietal lobe		1
Temporal lobe		1
Occipital lobe		-
Cerebellum		1
Brainstem		3
Other deep structures incl. basal ganglia		5
Generalized edema		1 (1)
Hydrocephalus		1 (1)
CNS malignancy		1 (1)
Other**		3 (4)
EEG performed	87	46 (53)
EEG findings suggestive of encephalitis	46	24 (52)

434 CT: Computed tomography. EEG: Electroencephalography. IQR: Interquartile ranges. MRI: Magnetic resonance
435 imaging. *Several lesions were present in some patients. All brain infarctions occurred within eight days except
436 for one which was diagnosed 74 days after admission. **Concomitant lesions suggestive of toxoplasmosis in
437 one patient (HIV positive), basilar aneurysm in one patient not considered VZV vasculitis, and cranial osteolytic
438 abnormalities in one patient
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Table 4. Treatment and outcome of 92 adult VZV encephalitis patients in Denmark from 2015-2019.

Summary of treatment and outcome

Variable	Obs	*N* (%) / median (IQR)
Treatment		
Intravenous acyclovir	92	92 (100)
Time to acyclovir administration (h)*	91	13.4 (5.2-46.3)
Duration of IV treatment (days)	88	14 (7-14)
Oral acyclovir/valacyclovir after IV treatment	90	43 (48)
Duration of oral acyclovir/valaciclovir after IV treatment (days)	42	11 (7-15)
Adjunctive dexamethasone	89	23 (26)
ICU admission	92	13 (14)
Outcome		
In-hospital mortality	92	4 (4)
1-month mortality	92	8 (9)
3-month mortality	92	10 (11)
Unfavorable outcome at discharge	91	63 (69)
Unfavorable outcome one month since discharge	83	46 (55)
Unfavorable outcome three months since discharge	80	41 (51)

Pre-existing comorbidity and outcome

Outcome	Obs	Pre-existing physical/cognitive deficits (%)	No pre-existing physical/cognitive deficits (%)	p-value
Death				
In-hospital mortality	92	3/46 (7)	1/46 (2)	0.31
1-month mortality	92	7/46 (15)	1/46 (2)	0.03
3-month mortality	92	7/46 (15)	3/46 (7)	0.18
Unfavorable outcome (GOS 1-4)				
At discharge	91	38/45 (84)	25/46 (54)	0.002
1-month since discharge	83	30/40 (75)	16/43 (37)	0.001
3-months since discharge	80	28/38 (74)	13/42 (31)	<0.001

Risk factors for unfavorable outcome (GOS 1-4) at discharge

Variable	Crude RR (95% CI)	Adj. RR (95% CI)
Age	1.02 (1.01-1.03)	1.02 (1.01-1.03)
Sex		
Male	Ref.	Ref.
Female	1.12 (0.85-1.48)	1.05 (0.80-1.38)
Vasculitis	1.39 (1.10-1.76)	1.38 (1.02-1.86)
Time to IV acyclovir treatment		
0-24 h	Ref.	Ref.
24-48 h	1.32 (0.97-1.80)	1.08 (0.79-1.47)
>48 h	1.22 (0.89-1.68)	1.25 (0.92-1.70)
GCS		
GCS 15	Ref.	Ref.
GCS <15	1.38 (1.06-1.80)	1.32 (1.01-1.73)
Adjuctive dexamethasone	0.94 (0.67-1.31)	0.95 (0.69-1.31)

GOS: Glascow Outcome Scale. ICU: Intensive care unit. IV: Intravenous. GCS: Glasgow coma scale.
*From time of admission

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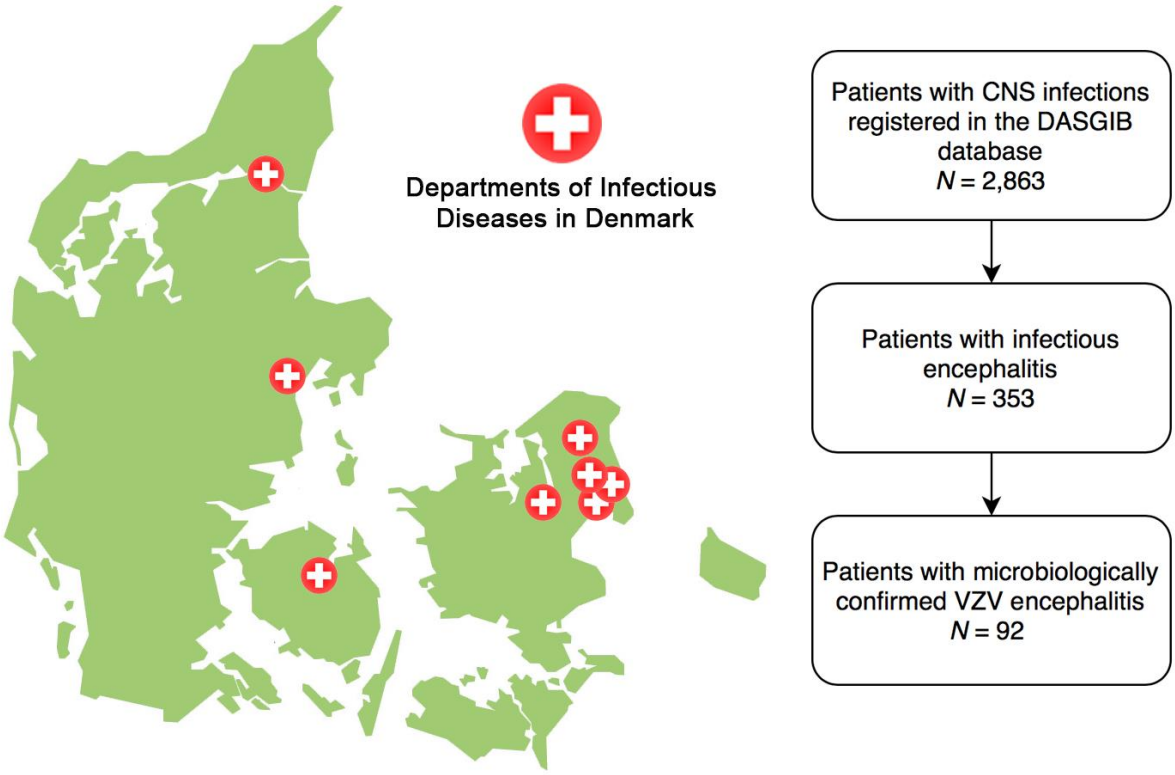
Figure legends:

Figure 1. The eight departments of infectious diseases in Denmark and the selection of VZV encephalitis patients from the DASGIB database.

448 **Figures**

449 Figure 1.



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