Characteristics and long-term prognosis of Danish residents with a positive intrathecal antibody index test for herpes simplex virus or varicella-zoster virus compared with individuals with a positive cerebrospinal fluid PCR: A nationwide cohort study

Platz, Isabella L.; Tetens, Malte M.; Dessau, Ram; Ellermann-Eriksen, Svend; Andersen, Nanna S.; Solholm Jensen, Veronika Vorobieva; Østergaard, Christian; Bodilsen, Jacob; Søgaard, Kirstine Kobberøe; Bangsborg, Jette; Yde Nielsen, Alex Christian; Møller, Jens Kjølseth; Lebech, Anne-Mette; Omland, Lars Haukali; Obel, Niels

Published in:
Clinical Microbiology and Infection

DOI (link to publication from Publisher):
10.1016/j.cmi.2023.11.004

Publication date:
2024

Document Version
Publisher's PDF, also known as Version of record

Clinical Microbiology and Infection 30 (2024) 240–246

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Characteristics and long-term prognosis of Danish residents with a positive intrathecal antibody index test for herpes simplex virus or varicella-zoster virus compared with individuals with a positive cerebrospinal fluid PCR: a nationwide cohort study

Isabella L. Platz [1,*], Malte M. Tetens [1], Ram Dessau [2,3], Svend Ellermann-Eriksen [4], Nanna S. Andersen [5,6], Veronika Vorobieva Solholm Jensen [7], Christian Østergaard [8], Jacob Bodilsen [9,10], Kirstine Kobberøe Søgaard [9,11], Jette Bangsborg [12], Alex Christian Yde Nielsen [13], Jens Kjølseth Møller [14], Anne-Mette Lebech [1,15], Lars Haukali Omland [1], Niels Obel [1,15]

[1] Department of Infectious Diseases, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark
[2] Department of Clinical Microbiology, Zealand University Hospital, Slagelse, Denmark
[3] Department of Regional Health Research, University of Southern Denmark, Odense, Denmark
[4] Department of Clinical Microbiology, Aarhus University Hospital, Aarhus, Denmark
[5] Department of Clinical Microbiology, Odense University Hospital, Odense, Denmark
[6] Research Unit of Clinical Microbiology, University of Southern Denmark, Odense, Denmark
[7] Department of Virus & Microbiological Special Diagnostics, Statens Serum Institut, Copenhagen, Denmark
[8] Department of Clinical Microbiology, Copenhagen University Hospital – Hvidovre Hospital, Copenhagen, Denmark
[9] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
[10] Department of Infectious Diseases, Aalborg University Hospital, Aalborg, Denmark
[11] Department of Clinical Microbiology, Aalborg University Hospital, Aalborg, Denmark
[12] Department of Clinical Microbiology, Copenhagen University Hospital - Herlev Hospital, Herlev, Denmark
[13] Department of Clinical Microbiology, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark
[14] Department of Clinical Microbiology, Vejle Hospital, University Hospital of Southern Denmark, Vejle, Denmark
[15] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

ARTICLE INFO

Article history:
Received 31 July 2023
Received in revised form
6 November 2023
Accepted 7 November 2023
Available online 13 November 2023

Editor: L. Kaiser

Keywords:
Central nervous system infections
Herpes simplex viruses
Intrathecal antibody index
PCR
Varicella-zoster virus

ABSTRACT

Objectives: We compared characteristics and outcomes of individuals who in the cerebrospinal fluid (CSF) were positive for herpes simplex virus (HSV) or varicella-zoster virus (VZV)-intrathecal antibody index test ([AI]-positive) vs. individuals who were PCR-positive for HSV type 1 (HSV1), type 2 (HSV2), and for VZV.

Methods: Nationwide cohort study of all Danish residents with positive CSF-AI or -PCR for HSV or VZV (1995–2021). We calculated short- and long-term risks as age-, sex-, and comorbidity-adjusted odds ratios (aOR), adjusted hazard ratios (aHR), and absolute risk differences with 95% CIs.

Results: Compared with individuals with positive PCR for HSV1 ($n = 321$), HSV2 ($n = 497$), and VZV ($n = 1054$), individuals with a positive AI for HSV ($n = 177$) and VZV ($n = 219$) had CSF pleocytosis less frequently (leucocyte count >10/μL: HSV-AI: 39%, VZV-AI: 52%, HSV1-PCR: 81%, HSV2-PCR: 92%, VZV-PCR: 83%), and were less frequently diagnosed with central nervous system infection ([aOR {95%CI}]: HSV-AI vs. HSV1-PCR: [0.1 {0.1, 0.2}], HSV-AI vs. HSV2-PCR: [0.1 {0.0, 0.1}], VZV-AI vs. VZV-PCR: [0.2 {0.2, 0.3}]). Individuals with a positive HSV-AI or VZV-AI had increased risk of demyelinating disease ([aOR {95%CI}; aHR {95%CI}]: HSV-AI vs. HSV1-PCR: [4.6 {0.9, 24.5}; aHR not applicable], HSV-AI vs. HSV2-PCR: [10.4 {2.3, 45.9}; 12.4 {2.3, 66.0}], VZV-AI vs. VZV-PCR: [aOR not applicable; 10.3 {1.8, 58.8}]). Disability pension was less frequent among HSV-AI than HSV1-PCR cohort members (5-year risk

* Corresponding author. Isabella L. Platz, Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK-2100, Copenhagen Ø, Denmark.
E-mail address: isabella.lykke.platz.01@regionh.dk (I.L. Platz).

https://doi.org/10.1016/j.cmi.2023.11.004

difference: −23.6%, 95%CI: −35.2, −11.8), and more frequent among VZV-AI than VZV-PCR cohort members (5-year risk difference: 16.8%, 95%CI: 5.0, 28.7).
Discussion: AI-positive individuals differ from PCR-positive individuals in several aspects. AI appears unspecific for current central nervous system infections. **Isabella L. Platz, Clin Microbiol Infect 2024;30:240**

Introduction

Herpes simplex virus (HSV) type 1 (HSV1), HSV type 2 (HSV2), and varicella-zoster virus (VZV) are important causes of central nervous system (CNS) infections [1,2]. HSV1 manifests primarily as encephalitis, HSV2 as meningitis [3,4], and VZV as encephalitis, meningitis, and vasculitis [5].

HSV1, HSV2, and VZV are detected in the cerebrospinal fluid (CSF) by PCR [6]. Danish guidelines recommend an intrathecal antibody index test (AI) for HSV and/or VZV if the PCR is negative and/or if VZV vasculitis is suspected [7,8].

A positive AI should be interpreted carefully because of low specificity [9]. Individuals with demyelinating disease often have positive AI for several pathogens including VZV and HSV [9–11]. Furthermore, a positive HSV-AI may persist years after HSV encephalitis [12].

PCR has a high sensitivity for HSV1, HSV2, and VZV in CSF, why CNS infection with these viruses in individuals with negative PCR presumably occurs infrequently [11,13]. Therefore, it is likely that in a PCR-negative population, a large proportion of HSV or VZV AIs will be positive even in absence of actual current infection. It remains unclear whether a positive HSV/VZV AI in absence of a positive CSF-PCR adds additional clinical information.

We aimed to investigate differences in baseline characteristics, CSF-markers, and outcomes among HSV−AI positive individuals and VZV−AI positive individuals compared with CSF-PCR positive individuals.

Methods

We performed a nationwide cohort study of individuals with a positive HSV-AI, VZV-AI, HSV1 CSF-PCR, HSV2 CSF-PCR, or VZV CSF-PCR between 1 January 1995 and 1 September 2021.

Setting

All Danish residents have access to tax-supported healthcare free of charge and are assigned a ten-digit personal identification number, which we used to track individuals in the Danish national registries [14].

Data sources

We obtained data on all CSF-AI IgG and CSF-PCR performed at Danish departments of clinical microbiology (Supplementary Appendix 1, Table S1).

We obtained data on sex, date of birth, emigration, immigration, loss-to-follow-up, and death from the Danish Civil Registration System [15] (Supplementary Appendix 1), data on biochemical analyses from the Danish Laboratory Database, established in 2008 [16], data on hospital diagnoses, and date of hospital contact from the Danish National Patient Registry [17], data on redemption of medication from the Danish National Prescription Registry [18], and data on reception of disability pension from The Employment Classification Module at Statistics Denmark [19].

Study population

We included all Danish residents with a first-time positive HSV-AI, VZV-AI, and/or CSF-PCR for HSV1, HSV2, or VZV. Date of study inclusion was date of the first positive AI or CSF-PCR.

We formed an HSV-AI cohort and a VZV-AI cohort, which included all individuals with a positive AI for HSV or VZV without a positive CSF-PCR for HSV1, HSV2, or VZV within 90 days of study inclusion (negative PCR or no PCR performed). We formed three comparison cohorts: (a) an HSV1-PCR cohort; (b) an HSV2-PCR cohort, (c) a VZV-PCR cohort, which included all individuals with a positive CSF-PCR for HSV1, HSV2, or VZV.

Because of inaccuracies, one centre discontinued AIs. Thus, we excluded results from this centre.

We excluded all individuals with a prior CNS infection and all individuals who had a positive CSF-test for other pathogens within 90 days after study inclusion.

Individuals who had both a positive AI and PCR within 90 days were categorized as CSF-PCR positive (HSV1-PCR = 15, HSV2-PCR = 7, and VZV-PCR = 60).

Outcomes

Outcomes were (a) short-term diagnoses of CNS infection; (b) short- and long-term mortality, incident diagnoses of organic psychiatric disorders, and demyelinating disease; (c) frequency of neurological outpatient contact; (d) frequency of hospital contacts because of epilepsy, and receipt of antiepileptic medication; and (e) receipt of disability pension. We defined diagnoses according to International Classification of Diseases, tenth revision codes (Table S2) and antiepileptic medication according to the Anatomical Therapeutic Chemical classification system (code N03).

Statistical analysis

Baseline characteristics

We identified all hospital diagnoses assigned to individuals in each cohort >180 days before study inclusion. Based on the diagnoses, we calculated the proportion of cohort members with a Charlson Comorbidity Index (CCI) score ≥2 [20], and previous outcomes of interest (Table S2).

We identified results of biochemical analyses performed after 2008. We calculated median CSF leucocyte count, protein, and glucose concentration. We calculated the proportion of cohort members with a CSF leucocyte count $>10 \times 10^6$/L, protein concentration >1 g/L, and glucose concentration <2 mmol/L.

We calculated the proportion of cohort members admitted to a department of neurology at study inclusion and time from hospital admission to first and diagnostic lumbar puncture (lumbar puncture with positive AI or CSF-PCR).

Risk analysis

We calculated short-term risk of CNS infection diagnosis, specific HSV or VZV CNS infection, and short- and long-term risk of

death, first-time organic psychiatric disorder, and demyelinating disease.

For short-term risks, we used logistic regression to calculate ORs for each outcome between 180 days before to 180 days after study inclusion. In the analyses of death, we calculated short-term risk between date of study inclusion and 180 days after study inclusion.

For long-term risk, we calculated time from 180 days after date of study inclusion to the outcome of interest, date of emigration, date of death, or end of follow-up on 1 September 2021, whichever came first. We used Cox-regression to calculate mortality rate ratios and hazard ratios.

We adjusted all analyses for age (categorical variable, grouped per 10 years), sex, and CCI-score (categorical variable, CCI >2 was categorized as 2). We used the change-in-estimate-principle only including covariates that changed the estimate more than 10% in the final model [21] (Table S3 for a detailed description of the models used).

Frequency analysis

We identified all hospital diagnoses, date of hospital admissions and discharges, and outpatient contact, antiepileptic medication redemption, and disability pension reception.

We calculated the proportion of cohort members with at least one outpatient contact at a department of neurology, hospital contact because of epilepsy, receipt of antiepileptic medication, and the proportion with disability pension per year from the last of 5 years before study inclusion, birth, or immigration until the first of 5 years after the date of study inclusion, emigration, 1 September 2021, death, or loss-to-follow-up. We used descriptive statistics and logistic regression to calculate absolute risk differences and ORs. We adjusted the ORs for age, sex, and CCI. The analyses of reception of disability pension included only individuals aged 20–60 years. We further performed the analyses of disability pension receipt separately for cohort members with and without a diagnosis of demyelinating diseases.

Sensitivity analysis

For each analysis, we performed a sensitivity analysis in which we excluded all AI-positive individuals who did not have a PCR performed.

Approval and ethics

Research based on registry data without direct patient interaction does not require individual consent according to Danish law. This study was approved by the Danish Data Protection Agency and the National Board of Health (RH-2015-285, I-Suite No.: 04297).

Results

Baseline characteristics

We included 177, 321, and 497 individuals in the HSV-AI, HSV1-PCR, and HSV2-PCR cohorts and 219 and 1054 individuals in the VZV-AI and VZV-PCR cohorts (Table 1). The cohorts differed with respect to sex and median age. HSV-AI and VZV-AI cohort members had lower CSF leucocyte count and protein concentration compared with the PCR cohorts. A larger proportion of AI cohort members were admitted to a department of neurology, and they had longer median time from admission to diagnostic lumbar puncture.

CNS infection

The short-term risk of a CNS-infection diagnosis was decreased among HSV-AI cohort members compared with HSV1-PCR and HSV2-PCR cohort members, and among VZV-AI cohort members compared with VZV-PCR cohort members (Table 2). Adjustment for age, sex, and CCI did not affect the estimates.

Table 1
Characteristics of individuals with positive HSV-AI, HSV1-PCR, HSV2-PCR, VZV-AI, and VZV-PCR at study inclusion

	HSV-AI cohort	HSV1-PCR cohort	HSV2-PCR cohort	VZV-AI cohort	VZV-PCR cohort
Total number	177	321	497	219	1054
Age (y)[a]	49 (35–65)	63 (45–73)	38 (28–50)	49 (36–67)	59 (31–77)
Female sex	97 (55)	164 (51)	362 (73)	123 (56)	522 (50)
Yearly taxable income[b]	229 (153–327)	206 (147–296)	252 (172–358)	245 (154–341)	205 (129–313)
Comorbidity[c]					
Charlson Comorbidity Index Score ≥2	32 (18)	85 (27)	67 (14)	48 (22)	332 (32)
Previous organic psychiatric disorder	≤3 (≤1)	≤3 (≤1)	≤3 (≤1)	4 (2)	12 (1)
Previous demyelinating disease	≤3 (≤1)	≤3 (≤1)	≤3 (≤1)	7 (3)	6 (1)
Leucocytes in CSF					
Number of individuals with test results	87	164	289	111	621
Leucocyte count (10×10^6/L)[a]	7 (3–22)	57 (16–131)	378 (166–666)	12 (5–33)	122 (26–329)
Number with leucocyte count >10×10^6/L	34 (39)	132 (81)	266 (92)	58 (52)	516 (83)
Protein in CSF					
Number of individuals with test results	85	161	273	109	596
Protein concentration (g/L)[a]	0.4 (0.3–0.6)	0.7 (0.4–1.1)	1.2 (0.8–1.5)	0.5 (0.4–0.6)	0.8 (0.5–1.2)
Number with protein concentration >1 g/L	8 (9)	42 (26)	167 (61)	9 (8)	206 (35)
Glucose in CSF					
Number of individuals with test results	86	159	280	105	596
Glucose concentration (mM)[a]	3.4 (3.1–3.9)	4.0 (3.2–4.9)	3.1 (2.7–3.5)	3.5 (3.1–3.9)	3.3 (2.9–3.8)
Number with glucose concentration <2 mM	2 (2)	3 (2)	4 (1)	3 (3)	11 (2)
Time from admission to first LP (d)[a]	0 (0–3)	0 (0–0)	0 (0–0)	0 (0–1)	0 (0–1)
Time from admission to diagnostic LP (d)[a]	1 (0–6)	0 (0–0)	0 (0–1)	1 (0–5)	0 (0–1)
Admitted to a department of neurology	90 (51)	83 (26)	76 (15)	116 (53)	285 (27)
Observation time (y)[a]	5 (2–10)	4 (1–10)	5 (3–11)	4 (1–11)	4 (2–8)
Total years of observation	1100	2022	3610	1300	5727

Characteristics of HSV-AI, HSV1-PCR, HSV2-PCR, VZV-AI, and VZV-PCR cohort members. Values are stated in number (%) unless otherwise stated. AI, intrathecal antibody index test; CSF, cerebrospinal fluid; HSV, herpes simplex virus; HSV1, HSV type 1; HSV2, HSV type 2; LP, lumbar puncture; VZV, varicella-zoster virus.

[a] Median (interquartile range).

[b] Median (interquartile range) in 1000 Danish Kroner. Reported on December 31, the year before study inclusion.

[c] On the basis of diagnoses assigned before 180 d before study inclusion.

Table 2
Short-term risk among individuals with positive HSV-AI, HSV1-PCR, HSV2-PCR, VZV-AI, and VZV-PCR

	HSV cohorts						
	HSV-AI, N (%)	HSV1-PCR, N (%)	OR (95% CI)	aOR (95% CI)[a]	HSV2-PCR, N (%)	OR (95%CI)	aOR (95% CI)[a]
CNS infection	82 (46)	286 (89)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	463 (93)	0.1 (0.0, 0.1)	0.1 (0.0, 0.1)
HSV CNS infection	43 (24)	245 (76)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	357 (72)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)
VZV CNS infection	11 (6)	26 (8)	0.8 (0.4, 1.6)	0.8 (0.4, 1.6)	32 (6)	1.0 (0.5, 2.0)	1.0 (0.5, 2.0)
Death[b]	20 (11)	70 (22)	0.5 (0.3, 0.8)	0.7 (0.4, 1.2)	25 (5)	2.4 (1.3, 4.4)	1.3 (0.6, 3.0)
Organic psychiatric disorders	≤3 (≤1)	17 (5)	0.2 (0.0, 0.9)	0.2 (0.0, 0.9)	≤3 (≤1)	1.9 (0.3, 11.4)	2.2 (0.4, 13.9)
Demyelinating disease	6 (3)	≤3 (≤1)	5.6 (1.1, 28.0)	4.6 (0.9, 24.5)	≤3 (≤1)	5.8 (1.4, 23.4)	10.4 (2.3, 45.9)

	VZV cohorts			
	VZV-AI, N (%)	VZV-PCR, N (%)	OR (95% CI)	aOR (95%CI)[a]
CNS infection	105 (48)	845 (80)	0.2 (0.2, 0.3)	0.2 (0.2, 0.3)
HSV CNS infection	10 (5)	91 (9)	0.5 (0.3, 1.0)	0.5 (0.3, 1.0)
VZV CNS infection	47 (22)	695 (66)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)
Death[b]	12 (6)	102 (10)	0.5 (0.3, 1.0)	0.9 (0.5, 1.8)
Organic psychiatric disorders	4 (2)	9 (1)	2.2 (0.7, 7.1)	2.2 (0.7, 7.1)
Demyelinating disease	34 (16)	≤3 (≤1)	NA[c]	NA[c]

Short-term risk of first-time diagnosis of CNS infection, HSV CNS infection, VZV CNS infection, death, organic psychiatric disorders, and demyelinating disease among HSV-AI, HSV1-PCR, HSV2-PCR, VZV-AI, and VZV-PCR cohort members. We calculated time from 180 d before study inclusion until 180 d after study inclusion.
AI, intrathecal antibody index test; aOR, adjusted odds ratios; CNS, central nervous system; HSV, herpes simplex virus; HSV1, HSV type 1; HSV2, HSV type 2; NA, not applicable; VZV, varicella-zoster virus.
[a] Adjusted for age, sex, and Charlson Comorbidity Index Score.
[b] From time of study inclusion.
[c] Not calculated because of too few events.

Mortality

The short- and long-term mortality was lower among HSV-AI and VZV-AI cohort members compared with HSV1-PCR and VZV-PCR cohort members and increased among HSV-AI cohort members compared with HSV2-PCR cohort members. However, after adjustment these differences almost disappeared (Tables 2 and 3).

Psychiatric disorders

We observed no substantial differences in risk of organic psychiatric disorders except that short- and long-term risks were decreased in the HSV-AI cohort compared with the HSV1-PCR cohort (Tables 2 and 3).

Demyelinating disease

The short- and long-term risks of demyelinating disease were substantially increased among AI cohort members compared with PCR cohort members (Tables 2 and 3). In the short-term, 16% of VZV-AI cohort members were diagnosed with a demyelinating disease compared with ≤1% of VZV-PCR cohort members.

Neurological outpatient contact

In the year of study inclusion, the proportion of cohort members with a neurological outpatient contact was higher in the HSV-AI cohort than in the HSV-PCR cohorts (Fig. 1, Table S4). After the first year, a larger proportion of HSV-AI cohort members had neurological outpatient contact than in the HSV2-PCR cohort.

After study inclusion, a larger proportion of cohort members in the VZV-AI cohort had neurological outpatient contacts than in the VZV-PCR cohort (Fig. 1, Table S4).

Epilepsy

A smaller proportion of HSV-AI cohort members had hospital contact because of epilepsy and receipt of antiepileptics than in the HSV1-PCR cohort. A slightly larger proportion of cohort members in the HSV-AI and VZV-AI cohorts had hospital contacts because of epilepsy and antiepileptic medication redemption than in the HSV2-PCR and VZV-PCR cohorts (Fig. 1, Table S4).

Disability pension

After study inclusion, the proportion of HSV-AI cohort members who received disability pension was lower than in the HSV1-PCR cohort (Fig. 1, Table S4), but did not differ substantially from the proportion of HSV2-PCR cohort members with disability pension.

After study inclusion, the proportion of cohort members with disability pension was higher in the VZV-AI cohort than in the VZV-PCR cohort (Fig. 1, Table S4). Among VZV-AI cohort members, the increased frequency of disability pension was slightly lower among individuals not diagnosed with demyelinating disease than among individuals diagnosed with demyelinating disease, but the frequency was still increased compared with the PCR-positive cohort members (data not shown).

Sensitivity analysis

Among HSV-AI and VZV-AI cohort members, 150 (85%) and 172 (78%) had a PCR performed. Exclusion of the AI-positive individuals with no PCR performed did not change the results (Tables S5 and S6 and Fig. S1).

Discussion

In this nationwide cohort study, HSV-AI and VZV-AI cohort members differed from PCR cohort members with respect to age, sex, CCI, and CSF inflammation. We observed no substantial differences in mortality, but AI cohort members had a lower rate of CNS-infection diagnoses and increased risk of demyelinating diseases. Epilepsy and disability pension receipt were more frequent among HSV1-PCR than HSV-AI cohort members and among VZV-AI than VZV-PCR cohort members.

Table 3
Long-term risk among individuals with positive HSV-AI, HSV1-PCR, HSV2-PCR, VZV-AI, and VZV-PCR

	HSV cohorts						
	HSV-AI, N (%)	HSV1-PCR, N (%)	HR (95% CI)	aHR (95% CI)[a]	HSV2-PCR, N (%)	HR (95%CI)	aHR (95% CI)[a]
Death	21 (13)	47 (19)	0.7 (0.4, 1.2)	1.1 (0.6, 1.8)	21 (4)	3.2 (1.7, 5.8)	1.4 (0.8, 2.6)
Organic psychiatric disorders	≤3 (≤1)	16 (8)	NA[b]	NA[b]	7 (2)	NA[b]	NA[b]
Demyelinating disease	5 (4)	≤3 (≤1)	NA[b]	NA[b]	≤3 (≤1)	8.2 (1.6, 42.5)	12.4 (2.3, 66.0)

	VZV cohorts			
	VZV-AI, N (%)	VZV-PCR, N (%)	HR (95% CI)	aHR (95%CI)[a]
Death	24 (12)	179 (19)	0.6 (0.4, 0.9)	0.8 (0.5, 1.3)
Organic psychiatric disorders	≤3 (≤1)	21 (2)	0.5 (0.1, 1.9)	0.6 (0.1, 2.6)
Demyelinating disease	4 (3)	≤3 (≤1)	11.6 (2.1, 63.4)	10.3 (1.8, 58.8)

Long-term risk of death, organic psychiatric disorders, and demyelinating disease among HSV-AI, HSV1-PCR, HSV2-PCR, VZV-AI, and VZV-PCR cohort members. We calculated time from 180 d after study inclusion.
AI, intrathecal antibody index test; HSV, herpes simplex virus; HSV1, HSV type 1; HSV2, HSV type 2; NA, not applicable; VZV, varicella-zoster virus.
[a] Adjusted for age, sex, and Charlson Comorbidity Index Score.
[b] Could not be calculated because of too few events.

The baseline characteristics, CSF-parameters, risk of epilepsy, and reception of disability pension, and mortality among HSV1-, HSV2-, and VZV-PCR positive individuals in our study are consistent with previous research [22–24].

CSF inflammation was lower in AI-positive individuals which suggests that these individuals are less likely to suffer from actual CNS infection than PCR-positive individuals [6,25], and agrees with our finding that AI-positive individuals were less frequently diagnosed with CNS infection.

Because AI is typically positive 1–2 weeks after infection, it is possible that the AI-positive individuals represent individuals with less severe disease who are diagnosed in later phases of the disease and thereby have a different prognosis [11].

Some AI tests may be false positives or positive because of a previous HSV or VZV infection. This could lead to positive AI tests in individuals who undergo diagnostic work-up for non-infectious CNS diseases including demyelinating diseases. In line with this, we observed a high prevalence of demyelinating diseases in the AI-positive cohorts, which has also been described in previous reports [9–11]. A substantial prevalence of false positive AIs will also explain why we observed differences in long-term prognosis and in use of contacts to departments of neurology between the AI-positive and PCR-positive cohorts.

We presume that a substantial proportion of the AI-positive individuals had the AI test performed as part of a diagnostic work-up of non-infectious neurological symptoms, which make our risk estimates prone to confounding by indication. However, almost 80% of AI-positive individuals had a PCR performed in combination with the AI. The absence of significant changes in the results after exclusion of those without a PCR performed suggests that indications for lumbar puncture do not solely account for the observed differences. It is possible that some AI cohort members were clinically suspected of CNS infection because of early symptoms of demyelinating disease. This agrees with the fact that symptoms of demyelinating diseases have been demonstrated even years before the diagnosis [26].

HSV encephalitis is associated with neuropsychological sequelae, epilepsy, and receipt of disability pension [22,23]. Because the HSV–AI analyses did not differentiate between HSV1 and HSV2 antibodies, some of the HSV–AI positive may have had HSV2 meningitis, which is associated with a benign prognosis [22]. Because there was no increased frequency of hospital contacts because of epilepsy in the AI-positive cohort, the larger proportion of VZV-AI cohort members with redemption of antiepileptic medication may be attributable to pain management and mood-stabilization rather than to epilepsy.

We observed differences in mortality between the five cohorts. The differences were minimized after adjustment for age-, sex-, and comorbidity which suggests that differences in mortality are partly because of baseline characteristic disparities.

The risk of diagnoses of non-infectious CNS diseases (e.g. demyelinating diseases) was increased in the VZV-AI cohort, which may explain the increased frequency of disability pension receipt and redemption of antiepileptics among VZV-AI positive individuals [27,28]. The increased receipt of disability pension among VZV-AI positive individuals may be exaggerated by VZV vasculopathies, because these are associated with stroke [29] and VZV-AI positivity with normocellular CSF [30]. Furthermore, it is possible that some individuals had a positive VZV-PCR because of herpes zoster (which generally has a good prognosis). This is also in accordance with the fact that one in five individuals in the VZV-PCR cohort were not diagnosed with a CNS infection.

Important strengths of our study are its large size, nationwide design, and the complete long-term follow-up of the cohorts. Also, we had access to national registries which provided complete data on death and comprehensive data on hospital contacts, neurological disorders, and social functioning.

We did not have access to clinical data from patient records, symptom duration, medical treatment, or the indication for lumbar puncture, why we could not stratify on these parameters. We partly mitigated this limitation by inclusion of results of CSF-analyses, by use of diagnoses assigned shortly within the time of lumbar puncture, and by performing a sensitivity analysis with exclusion of individuals with no preceding PCR.

We conclude that individuals with positive HSV-AI and VZV-AI have different characteristics and prognosis relative to individuals with a positive CSF-PCR. AI-positive individuals are less likely to have CSF inflammation, are less frequently diagnosed with a CNS infection, and have higher risk of demyelinating disease. A positive AI seems to be unspecific for a current HSV or VZV CNS infection and should be interpreted in combination with the clinical presentation.

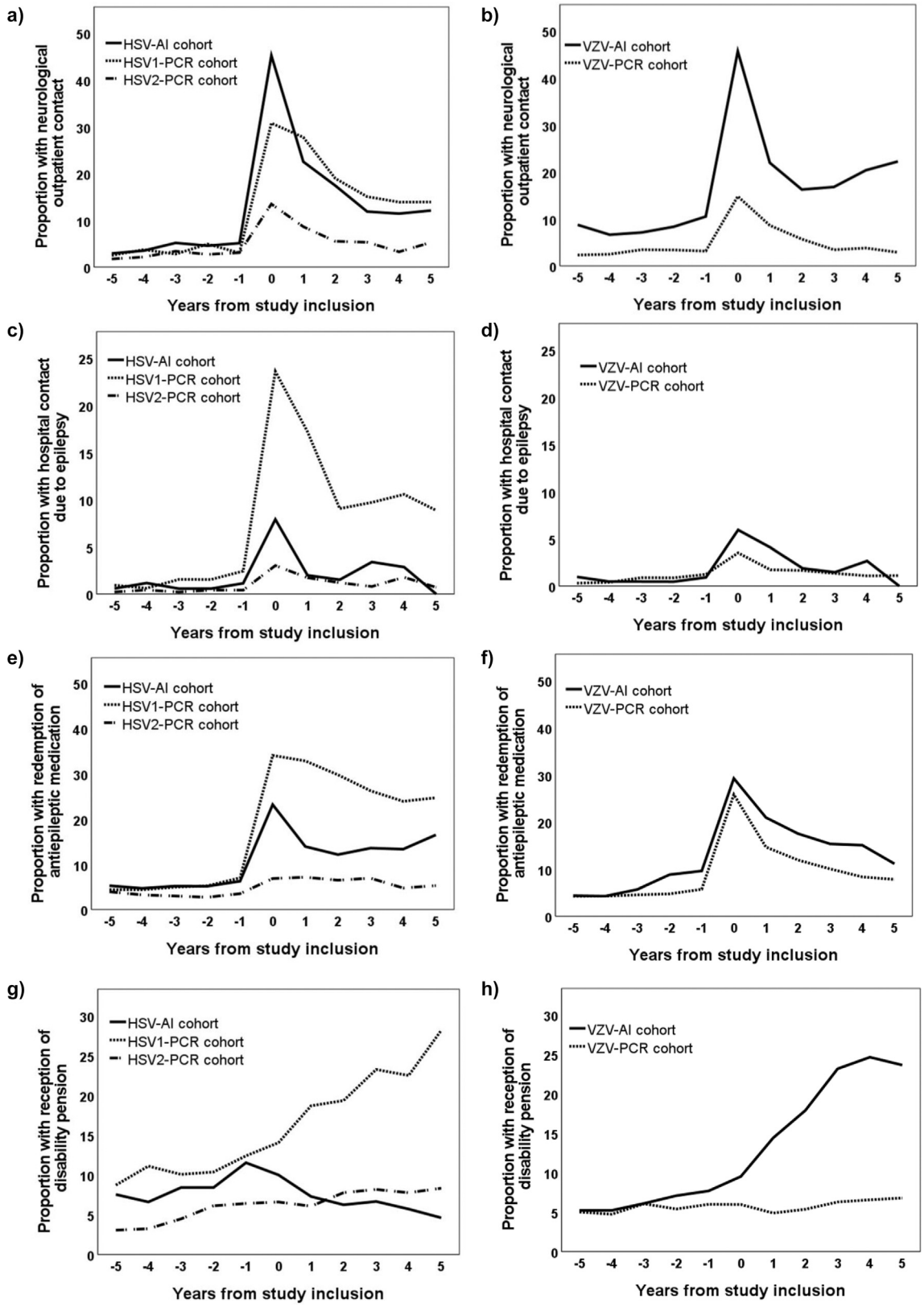

Fig. 1. Proportion with neurological outpatient contacts, hospital contacts because of epilepsy, receipt of antiepileptic medicine, and reception of disability pension. Proportion with neurological outpatient hospital contact per year for (a) HSV-AI (full line), HSV1-PCR (dots) and HSV2-PCR cohort members (dot-line-dot) and (b) VZV-AI (full line) and VZV-PCR cohort members (dots). Proportion with hospital contacts because of epilepsy per year for (c) HSV-AI (full line), HSV1-PCR (dots), and HSV2-PCR cohort members (dot-line-dot) and (d) VZV-AI (full line) and VZV-PCR cohort members (dots). Proportion with receipt of antiepileptic medicine per year for (e) HSV-AI (full line), HSV1-PCR (dots), and HSV2-PCR cohort members (dot-line-dot) and (f) VZV-AI (full line) and VZV-PCR cohort members (dots). Proportion with reception of disability pension per year for (g) HSV-AI (full line), HSV1-PCR (dots), and HSV2-PCR cohort members (dot-line-dot) and (h) VZV-PCR (dots). The figures demonstrate time from 5 y to 5 y after study inclusion.
AI, intrathecal antibody index test; HSV, herpes simplex virus; HSV1, HSV type 1; HSV2, HSV type 2; VZV, varicella-zoster virus.

Author contributions

ILP: conceptualization, formal analysis, writing—original draft, visualization. RD, SE-E, NSA, VVSJ, CØ, JB, KKS, JB, ACYN, and JKM: investigation, resources, data curation, writing, reviewing and editing. MMT, LHO, and NO: conceptualization, data curation, formal analysis, writing—review and editing. MMT, LHO, A-ML, and NO: supervision, project administration, visualization. A-ML: conceptualization, writing—review and editing. All authors amended and approved the final version of the manuscript.

Transparency declaration

A-ML reports speakers' honorarium/travel grants/advisory board activity and unrestricted grant from Gilead, speakers honorarium/travel grants from GSK, speaker's honorarium/advisory board activity from Pfizer outside this work. RBD reports support for attending meetings and/or travel for ECCMID2023 from ESCMID, participation in advisory board meeting for Pfizer, Amsterdam 2022, and participation in Chair Industry Session ECCMID 2023 outside this work. All other authors have no conflicts of interest to declare. The study was supported by the Danish Council for Independent Research, grant number [2034-00100B]: and Preben og Anne Simonsens Fond. The funders had no role in the preparation, design, analysis, or reporting of this study.

Data availability

The ethical approval of this study from the Danish Data Protection Agency states that the data used in this article cannot be publicly shared. Upon reasonable request to the corresponding author, the data is accessible at our institution.

Acknowledgements

Part of the data in this study was presented at the 33rd European Conference of Clinical Microbiology and Infectious Diseases in April 2023 in Copenhagen, Denmark.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2023.11.004.

References

[1] Koskiniemi M, Rantalaiho T, Piiparinen H, von Bonsdorff CH, Farkkila M, Jarvinen A, et al. Infections of the central nervous system of suspected viral origin: a collaborative study from Finland. J Neurovirol 2001;7:400–8. https://doi.org/10.1080/135502801753170255.

[2] McGill F, Griffiths MJ, Bonnett LJ, Geretti AM, Michael BD, Beeching NJ, et al. Incidence, aetiology, and sequelae of viral meningitis in UK adults: a multicentre prospective observational cohort study. Lancet Infect Dis 2018;18:992–1003. https://doi.org/10.1016/S1473-3099(18)30245-7.

[3] Moon SM, Kim T, Lee EM, Kang JK, Lee SA, Choi SH. Comparison of clinical manifestations, outcomes and cerebrospinal fluid findings between herpes simplex type 1 and type 2 central nervous system infections in adults. J Med Virol 2014;86:1766–71. https://doi.org/10.1002/jmv.23999.

[4] Omland LH, Vestergaard BF, Wandall JH. Herpes simplex virus type 2 infections of the central nervous system: a retrospective study of 49 patients. Scand J Infect Dis 2008;40:59–62. https://doi.org/10.1080/00365540701509881.

[5] Gilden D, Nagel M, Cohrs R, Mahalingam R, Baird N. Varicella zoster virus in the nervous system. F1000Res 2015;4:F1000. https://doi.org/10.12688/f1000research.7153.1.

[6] Venkatesan A, Tunkel AR, Bloch KC, Lauring AS, Sejvar J, Bitnun A, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. Clin Infect Dis 2013;57:1114–28. https://doi.org/10.1093/cid/cit458.

[7] [updated 9 April] Rekommandationer for udredning og behandling af viral meningitis hos voksne. 2018. https://www.infmed.dk/guidelines#viral_meningitis_(2018).pdf. [Accessed 20 June 2023].

[8] Vejledning til initial behandling af infektiøs encefalitis hos voksne [updated 27 August], https://www.infmed.dk/guidelines#encefalitis_2018.pdf. [Accessed 25 June 2023].

[9] Linde A, Klapper PE, Monteyne P, Echevarria JM, Cinque P, Rozenberg F, et al. Specific diagnostic methods for herpesvirus infections of the central nervous system: a consensus review by the European Union Concerted Action on Virus Meningitis and Encephalitis. Clin Diagn Virol 1997;8:83–104. https://doi.org/10.1016/s0928-0197(97)00015-9.

[10] Jacobi C, Lange P, Reiber H. Quantitation of intrathecal antibodies in cerebrospinal fluid of subacute sclerosing panencephalitis, herpes simplex encephalitis and multiple sclerosis: discrimination between microorganism-driven and polyspecific immune response. J Neuroimmunol 2007;187:139–46. https://doi.org/10.1016/j.jneuroim.2007.04.002.

[11] Shamier MC, Bogers S, Yusuf E, van Splunter M, Ten Berge J, Titulaer M, et al. The role of antibody indexes in clinical virology. Clin Microbiol Infect 2021;27:1207–11. https://doi.org/10.1016/j.cmi.2021.03.015.

[12] Vandvik B, Skoldenberg B, Forsgren M, Stiernstedt G, Jeansson S, Norrby E. Long-term persistence of intrathecal virus-specific antibody responses after herpes simplex virus encephalitis. J Neurol 1985;231:307–12. https://doi.org/10.1007/BF00313707.

[13] Grahn A, Studahl M. Varicella-zoster virus infections of the central nervous system – prognosis, diagnostics and treatment. J Infect 2015;71:281–93. https://doi.org/10.1016/j.jinf.2015.06.004.

[14] Schmidt M, Schmidt SAJ, Adelborg K, Sundboll J, Laugesen K, Ehrenstein V, et al. The Danish health care system and epidemiological research: from health care contacts to database records. Clin Epidemiol 2019;11:563–91. https://doi.org/10.2147/CLEP.S179083.

[15] Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish civil registration system. A cohort of eight million persons. Dan Med Bull 2006;53:441–9.

[16] Poulsen DT. Dokumentation af labdatabasens forskertabel. 2018. https://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-sundhedsregistre/doedsaarsager-og-biologisk-materiale/laboratoriedatabasen. [Accessed 13 November 2022].

[17] Lynge E, Sandegaard JL, Rebolj M. The Danish national patient register. Scand J Public Health 2011;39:30–3. https://doi.org/10.1177/1403494811401482.

[18] Pottegard A, Schmidt SAJ, Wallach-Kildemoes H, Sorensen HT, Hallas J, Schmidt M. Data resource profile: the Danish national prescription registry. Int J Epidemiol 2017;46:798-f. https://doi.org/10.1093/ije/dyw213.

[19] Baadsgaard M, Quitzau J. Danish registers on personal income and transfer payments. Scand J Public Health 2011;39:103–5. https://doi.org/10.1177/1403494811405098.

[20] Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 2011;173:676–82. https://doi.org/10.1093/aje/kwq433.

[21] Greenland S. Modeling and variable selection in epidemiologic analysis. Am J Public Health 1989;79:340–9. https://doi.org/10.2105/ajph.79.3.340.

[22] Hansen AE, Vestergaard HT, Dessau RB, Bodilsen J, Andersen NS, Omland LH, et al. Long-term survival, morbidity, social functioning and risk of disability in patients with a herpes simplex virus type 1 or type 2 central nervous system infection, Denmark, 2000-2016. Clin Epidemiol 2020;12:745–55. https://doi.org/10.2147/CLEP.S256838.

[23] Hjalmarsson A, Blomqvist P, Skoldenberg B. Herpes simplex encephalitis in Sweden, 1990-2001: incidence, morbidity, and mortality. Clin Infect Dis 2007;45:875–80. https://doi.org/10.1086/521262.

[24] Lee GH, Kim J, Kim HW, Cho JW. Herpes simplex viruses (1 and 2) and varicella-zoster virus infections in an adult population with aseptic meningitis or encephalitis: a nine-year retrospective clinical study. Medicine (Baltimore) 2021;100:e27856. https://doi.org/10.1097/MD.0000000000027856.

[25] McGill F, Griffiths MJ, Solomon T. Viral meningitis: current issues in diagnosis and treatment. Curr Opin Infect Dis 2017;30:248–56. https://doi.org/10.1097/QCO.0000000000000355.

[26] Fernandez O, Fernandez V, Arbizu T, Izquierdo G, Bosca I, Arroyo R, et al. Characteristics of multiple sclerosis at onset and delay of diagnosis and treatment in Spain (the Novo Study). J Neurol 2010;257:1500–7. https://doi.org/10.1007/s00415-010-5560-1.

[27] Landfeldt E, Castelo-Branco A, Svedbom A, Lofroth E, Kavaliunas A, Hillert J. Sick leave and disability pension before and after diagnosis of multiple sclerosis. Mult Scler 2016;22:1859–66. https://doi.org/10.1177/1352458516667567.

[28] Allen AN, Seminog OO, Goldacre MJ. Association between multiple sclerosis and epilepsy: large population-based record-linkage studies. BMC Neurol 2013;13:189. https://doi.org/10.1186/1471-2377-13-189.

[29] Teasdale TW, Engberg AW. Disability pensions in relation to stroke: a population study. Brain Inj 2002;16:997–1009. https://doi.org/10.1080/02699050210154240.

[30] Nagel MA, Cohrs RJ, Mahalingam R, Wellish MC, Forghani B, Schiller A, et al. The varicella zoster virus vasculopathies: clinical, CSF, imaging, and virologic features. Neurology 2008;70:853–60. https://doi.org/10.1212/01.wnl.0000304747.38502.e8.