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Herpes simplex virus 2 meningitis in adults:

A prospective, nationwide, population-based cohort study

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Summary: Using a nationwide and population-based clinical database, HSV-2 meningitis was characterized by meningeal symptoms and occurred mainly in younger females. Unfavorable outcome was common and was not associated with sex, age, immune-compromise, or CSF leukocyte count.

ABSTRACT

Background. Data on the clinical presentation are scarce and prognostic factors of Herpes simplex virus type 2 (HSV-2) meningitis remain unknown.

Methods. Prospective, nationwide, population-based database identifying all adults treated for HSV-2 meningitis at departments of infectious diseases in Denmark from 2015-2020. Unfavorable outcome was defined as Glasgow Outcome Scale (GOS) score of 1-4 and extended GOS score of 1-6. Modified Poisson regression was used to compute relative risks with 95% confidence intervals (RR, 95% CI) for unfavorable outcome.

Results. HSV-2 meningitis was diagnosed in 205 cases (76% female, median age 35 [IQR 27-49]) yielding an incidence of 0.7/100,000/year. Common symptoms were headache 195/204 (95%), photo/phonophobia 143/188 (76%), and neck stiffness 106/196 (54%). Median time to lumbar puncture was 2.0 hours (IQR 1-4.8) and cerebrospinal fluid (CSF) leukocyte count was $360x10^6$/L (IQR 166-670) with a mononuclear predominance of 97% (IQR 91-99). Lumbar puncture was preceded by brain imaging in 61/205 (30%). Acyclovir/valaciclovir was administered in 197/205 (96%) cases for a median of 10 days (IQR 7-14).

Unfavorable outcome was observed in 64/205 (31%) at discharge and 19/181 (11%) after six months and was not associated with female sex (RR 1.08, 95% CI 0.65-1.79), age ≥35 years (1.28, 0.83-1.97), immuno-compromise (1.07, 0.57-2.03), or CSF leukocyte count >$1,000x10^6$/L (0.78, 0.33-1.84).

Conclusions. HSV-2 meningitis often presented as meningeal symptoms in younger females. Unfavorable outcome at discharge was common and was not associated with sex, age, immune-compromise, or CSF leukocyte count. Sequelae persisted beyond six months in one tenth of patients.

Keywords: Herpes simplex virus 2, HSV-2, meningitis, adults, virus, nationwide, cohort, population-based, acyclovir, prognostic factors, incidence, prognosis, risk factors

INTRODUCTION

Herpes simplex virus type 2 (HSV-2) usually causes genital infection with mucocutaneous lesions or may be asymptomatic. Previous studies suggest that the infection is common among adults with seroprevalences ranging from 4% to 24% in European countries.[1–4] HSV-2 is also an important cause of meningitis either during primary infection or by (recurrent) reactivation of dormant virus within the central nervous system (CNS).[1,5,6]

Viral meningitis occurs in approximately 2.7 to 3.7/100,000/year and HSV-2 has been shown to be the third most frequent etiology in Northern Europe.[7–9] However, almost all previous studies on the clinical presentation and outcome of HSV-2 meningitis are restricted to single-centers with limited sample sizes and incomplete follow-up.[5,9–16] In addition, although viral meningitis may cause prolonged neurocognitive symptoms,[8,17] prognostic factors for unfavorable outcome remain unclear and have not been examined in adjusted analyses.

Using a prospective, nationwide, and population-based database,[18] this study aimed to describe the incidence, clinical presentation, management, outcome, and prognostic factors for unfavorable outcome in Danish adults with HSV-2 meningitis from 2015 through 2020.

METHODS

Setting, data source and study population

In Denmark, medical care is tax-financed and provided free of charge for the entire Danish population (5.8 million).[19] According to the Danish Board of Health, adults with CNS infections should be treated at departments of infectious diseases.[20]

The Danish Study Group of Infections of the Brain (DASGIB) is a nationwide scientific collaboration between departments of infectious diseases in Denmark (Suppl. Figure 1).[7,18] Since January 1 2015, DASGIB members have prospectively registered all adults (≥18 years of age) diagnosed with CNS infections at the involved study sites in a database. Completeness of reported CNS infections is ensured by annual searches using a standardized list of relevant International Classification of Diseases 10th revision diagnosis codes or medical record review of all patients with cerebrospinal fluid (CSF) leukocytosis. The database is managed using the Research electronic data capture (REDcap) software hosted by the North Denmark Region.[21]

This study included all adults (≥18 years of age) with HSV-2 meningitis registered in the DASGIB database from January 1, 2015, through December 31, 2020. HSV-2 meningitis was defined as a clinical presentation suggestive of viral meningitis (e.g. headache, neck stiffness, fever, photophobia) combined with CSF pleocytosis (>10 x 10^6/L) and either 1) Detection of HSV-2 by polymerase chain reaction (PCR) in CSF or genital lesions, 2) Positive intrathecal antibody ratio, or 3) Previously documented HSV-2 meningitis and no other diagnosis considered more likely given all available information.[18] HSV intrathecal antibody ratios were performed at Statens Serum Institut[22] and the Department of Clinical Microbiology at Hvidovre University Hospital,[23] Copenhagen, using an ELISA assay corrected for the total amount of protein in paired CSF and blood samples. Patients with encephalitis were not included.[24]

Data collection in DASGIB was approved by legal authorities of the North Denmark Region (local no. 2016-180) and the Danish Board of Health (3-3013-2579/1). In Denmark, patient consent or approval from an Ethics Committee is not required for this type of study.

Patient data

Data retrieved from the DASGIB database included baseline demographics, information on pre-existing comorbidities, time and place of admission, tentative diagnosis, details on the

clinical presentation at admission, diagnostic procedures, laboratory analyses, radiological examinations, and antiviral treatment. Immuno-compromise was defined as diagnosis of any type of cancer (except non-melanoma skin cancer), diabetes mellitus, HIV, asplenia, immuno-suppressive therapy, intravenous substance abuse, or primary immunodeficiency. Electronic medical records were used to obtain time of hospital admission (including ambulance and emergency records), lumbar puncture, diagnostic imaging, and antiviral treatment.

Outcome assessment

Using all available information in the medical records, outcome was assessed at discharge and after 1-, 3-, and 6-months of follow-up according to the Glasgow Outcome Scale (GOS): 1) Death; 2) A 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 (Table 1).[25,26]

The patient files were reviewed retrospectively for supplementary information on sequelae at one month after discharge as noted in the medical records. During this review, patients were also categorized according to the extended Glasgow outcome scale (GOSE) in order to describe minor but potentially relevant changes in those with good recovery: 1) Death; 2) Unresponsive and speechless; 3) Needs full assistance in in activities of daily life (ADL); 4) Needs partial assistance in ADL; 5) Independent but cannot resume work/school or all previous social activities; 6) Some disability exists but can partly resume work or previous activities; 7) Minor physical or mental deficits that affect daily life; 8) Full recovery or minor symptoms that do not affect daily life.[25,26]

Statistical analysis

Categorical variables were presented as n/N (%) to account for missing variables and continuous variables as medians with interquartile ranges (IQR). Continuous variables were compared using the Mann-Whitney rank sum test. The incidence of HSV-2 meningitis was

calculated as the mean number of cases per year during the study period divided by the population of adults ≥18 years of age in Denmark on January 1, 2020 (n=4,666,625).[19]

For all HSV-2 meningitis patients admitted at Aalborg University Hospital and Aarhus University Hospital from 2015 through 2019 (n=41), separate agreement levels of GOS and GOSE scores at discharge by two independent researchers (MTS and AJ) were examined by Cohen's kappa correlation score using the CFOUT Stata module.[27] The level of agreement was defined as 100% when scores were identical, 80% if scores differed by one level, and 0% if scores differed >1 level. A similar analysis was conducted adding a weighting of 50% if scores differed by two levels.[28]

For cases with missing GOS/GOSE during follow-up, last observation was carried forward for GOS 5 and GOSE 7-8. Unfavorable outcome was defined as GOS 1-4. Based on prior studies and presumed relevance, modified Poisson regression analysis was used to compute relative risk (RR) with 95% confidence interval (95% CI) of unfavorable outcome at discharge and adjusted for sex, age ≥35 years, CSF leukocyte count (0-99, 100-499, 500-999, ≥ 1000 ^10^6), and immune-compromise (yes/no).[29–32] A post-hoc analysis was also conducted examining the RR for unfavorable outcome at six months adjusted for age +/-35 years, sex, previous viral meningitis, immune-compromise, and symptom duration (0-1, 2-3, 4-5, and ≥6 days).

All statistical analysis was performed using Stata/MP® version 16 (StataCorp LLC, College Station, TX, USA).

RESULTS

During the six-year study period, 205 episodes of HSV-2 meningitis in 191 patients were included corresponding to an incidence of 0.7/100,000/year. The median age at diagnosis was 35 years (IQR 27-49) and 156/205 (76%) were female (Table 2).

Previous viral meningitis was reported by 63/205 (31%) and 83/175 (47%) had a history of genital herpes. Immuno-compromise was present in 19/205 (9%) patients. The median age of the 19 immuno-comprised individuals was 53 year (IQR 43-59) compared with 34 years (IQR 26-47) in 186 immuno-competent individuals (Figure 1, p=0.006). The median duration of symptoms was 1 day (IQR 1-3). Symptoms at admission included headache in 195/204 (95%), photo- or phonophobia in 143/188 (76%), nausea/vomiting in 145/200 (73%), and neck stiffness in 196/205 (54%). A history of fever before admission was described by 135/183 (74%).

The median C-reactive protein (CRP) was 3 mg/L (IQR 1-6) and blood leukocyte count was $8.3x10^9$/L (IQR 6.7-10.5). In the CSF, the median leukocyte count was $360x10^6$/L (IQR 166-670) with a mononuclear leukocyte count of $342x10^6$/L (IQR 147-620). The median protein concentration was 1.1 g/L (IQR 0.8-1.5), CSF:plasma glucose ratio was 0.52 (IQR 0.45-0.59), and CSF lactate was 3.1 mmol/L (IQR 2.6-3.9).

The diagnosis of HSV-2 meningitis was established by (in hierarchical order) a positive PCR for HSV-2 in the CSF in 180/205 (88%), positive intrathecal HSV antibody ratio in 13/205 (6%), positive PCR of genital lesion combined with meningism and CSF pleocytosis in 9/205 (4%), and viral meningitis in patients previously diagnosed with HSV-2 meningitis in 3/205 (1%).

Brain imaging using computed tomography (CT) or magnetic resonance imaging (MRI) was performed in 90/205 cases (44%). All patients had normal imaging findings except findings of optic neuritis, CNS malignancy, and subdural hematoma in one patient each. The median time from admission to lumbar puncture was 2.0 hours (IQR 1.0-4.8) and was preceded by brain imaging in 61/205 (30%). When brain imaging preceded lumbar puncture, the median time to lumbar puncture was 4.5 hours (IQR 2.8-7.5) compared with 1.3 hours (IQR 0.7-2.9) if brain imaging was done afterwards or not at all (p<0.001).

Antiviral treatment with intravenous (IV) acyclovir or oral valacyclovir was administered in 197/205 (96%) cases at a median of 4.9 hours (IQR 2.3-11.8) after admission. IV acyclovir was followed by valacyclovir in 145/197 (74%) of cases, whereas 20/197 (10%) and 32/197 (16%) were treated exclusively with either IV acyclovir or valacyclovir. The overall median total duration of therapy was 10 days (IQR 7-14).

Double data entry showed a discrepancy rate of 9% in GOS and GOSE scores respectively at discharge in a subgroup of 41 patients subjected to Cohen's kappa analysis by two independent researchers. The corresponding correlation score was 90% regardless of weighting algorithm.

Unfavorable outcome according to the GOS score was observed in 64/205 (31%) at discharge and decreased to 44/197 (22%) after 1-month, 36/192 (19%) after 3-months, and 19/181 (11%) after 6-months of follow-up (Table 3). All cases with unfavorable outcome had GOS 4 except one patient also diagnosed with Burkitt's lymphoma and HIV during admission who was categorized as GOS 3 at discharge and throughout follow-up. Most patients categorized with moderate disability using GOS were classified as upper moderate disability according to E-GOS. For patients categorized as good recovery by GOS, about half were characterized as upper good recovery within 1-month of follow-up which increased to about two thirds at 3- and 6-months of follow-up. Any sequelae was reported at 1-month follow-up in 101/205 (49%) and included tiredness 60/105 (57%), headache 66/117 (56%), fatigue 42/90 (47%), concentration difficulties 37/96 (39%), forgetfulness 28/91 (31%), sleep disturbances 14/77 (18), and dizziness 9/70 (13%). Both the GOS and GOSE-scores consistently demonstrated improved scores during follow-up.

Adjusted analyses showed a RR of unfavorable outcome at discharge of 1.08 (95% CI 0.65-1.79) in females, 1.28 (95% CI 0.83-1.97) in age ≥35 years, 1.07 (0.57-2.03)

in immuno-compromised individuals, and 0.78 (95% CI 0.33-1.84) in those with CSF leukocyte count >1,000x10^6/L (Table 4). In a post-hoc analysis, the RR for an

unfavorable outcome at six months was 3.12 (1.26-7.70) in patients with symptom duration ≥6 days and 0.24 (0.06-0.98) in those with previous viral meningitis when adjusted for age +/-35 years, sex, and immuno-compromise.

DISCUSSION

This study included 205 cases of HSV-2 meningitis in 191 adults yielding an annual incidence of 0.7/100,000 in Denmark during the study period. Cases were primarily young, previously healthy females presenting with meningeal symptoms. Unfavorable outcome at discharge was observed in a third of patients and steadily decreased during the following six months. Neither age, sex, immuno-compromise, nor CSF leukocyte count were found to be independent prognostic factors at discharge. A post-hoc adjusted analysis suggested that prolonged symptom duration may increase risk of unfavorable outcome after 6 months, whereas previous viral meningitis seemed to decrease this risk.

This is the first study to prospectively assess the incidence rate of HSV-2 meningitis in adults using a nationwide and population-based clinical database. The incidence in the current study was consistent with estimates from an English multicenter study of 0.8/100,000/year,[8] and higher than the observed 0.26/100.000/year in a previous Danish study from 1999 through 2003, *i.e.* before routine use of PCR for HSV-2 in CSF in Denmark.[10] The relatively young age distribution and predominance of females as well as the frequency of classic meningeal symptoms was comparable to corresponding observations in other studies.[9–12,33] The proportion of patients with pre-existing immuno-compromising conditions were also in line with another Danish study (9% vs. 6%).[10]

The median time from admission to lumbar puncture was 2.0 hours, which can be considered a proxy of time from admission until diagnosis. Early diagnosis is crucial in preventing excess cranial scans as well as unnecessary antibiotic and steroid treatment. Moreover, it is important for timely initiation of relevant treatment, determination of prognosis, and may prevent prolonged hospitalization.[8] In almost half of the cases, brain imaging was

performed during admission. Since the study population consisted mainly of young adults with a GCS of 15 and without any focal neurologic deficits, the frequent use of brain imaging seems unnecessary in terms of risk of cancer induced by radiation and healthcare expenditures. Still, the use of brain imaging in our cohort was moderate compared with other studies.[8,12,14]

The Danish national guideline emphasizes the overall lack of evidence for effectiveness of antivirals as well as treatment duration for viral meningitis.[34] However, acyclovir or valacyclovir is recommended if HSV or Varicella zoster virus is confirmed. Despite the nationwide design and data collection over five years, the limited number of patients and risk of confounding by indication (*i.e.* patients with less severe disease are more likely not to receive treatment) precluded analyses of the effect of antiviral treatment, including route of administration, on outcome.

Unfavorable outcome was found in 31% of cases at discharge and in 11% at six months of follow-up in this study. Use of the GOSE-score allowed a more detailed characterization of patients and suggested continuing mild disability, mainly due to neuropsychological and neurocognitive impairment, in some patients despite improvement with time. These observations are consistent with previous studies documenting similar types and duration of sequelae that may substantially affect daily living.[10,15] However, since GOS and GOSE mainly summarize social functioning, further detailed characterizations of patients with persisting cognitive impairment are required to improve our understanding and better support rehabilitation. Of note, a favorable long-term prognosis after HSV-2 CNS infection in terms of mortality, employment status, and risk of disability pension has been observed in a recent Danish registry-based study.[35] A number of prognostic factors were also examined in the current study, but none were found to be significantly associated with unfavorable outcome at discharge in a pre-specified adjusted analysis. However, a post-hoc adjusted analysis suggested a protective effect of previous viral meningitis on risk of unfavorable outcome after six months and a worse prognosis in those with symptom duration ≥6 days at admission. This warrants further exploration in other settings and could be due to immunological conditioning within the CNS, psychological adaptation to illness, or improved diagnosis including timely treatment with acyclovir.

HSV-2 infection has previously been shown to be more frequent in females compared with males. Several factors including increased genital mucosal surface area, transmission from asymptomatic males, differences in healthcare seeking behavior, and immunological response to viral infections may account some of these observations.[3,36–38] However, female sex was not associated with an adverse outcome of HSV-2 meningitis in the current study, which is in contrast to a recent publication on enterovirus meningitis.[39]

This study has limitations. Although the Danish Board of Health requires that treatment of CNS infections should involve infectious diseases specialists, some patients might have been diagnosed outside departments of infectious diseases or managed at home. This would lead to an underestimation of estimates of incidence. On the other hand, intrathecal antibody ratios are primarily used for encephalitis and have not been formally assessed for diagnosis of HSV-2 meningitis,[40] which could lead to an overestimation of the incidence if the specificity was low. GOS and GOSE scores have not been validated for HSV-2 meningitis and may lack sensitivity to mild neurocognitive impairment. Furthermore, categorizations were performed by different clinicians which may predispose to errors in registration. However, the rate of agreement of double data entry was 91% and inter-observer agreement of GOSE by Cohen's kappa analysis showed a very high correlation score of 90% in all included patients from two study sites. Missing data was present due to changes in hospital IT-systems during the study period, lack of systematic descriptions of sequelae, and not all patients had follow-up after discharge. Finally, the generalizability of the results is considered to be high due to the nationwide and population-based design.

Conclusion

This study shows that HSV-2 meningitis is a frequent infection among young and middle-aged adults, especially in females with a yearly incidence of 0.7/100,000. The clinical presentation was dominated by headache, photo- and phonophobia, nausea/vomiting and neck stiffness. Unfavorable outcome was frequent at discharge and was not associated with age, sex, immuno-compromise, or CSF leukocyte count. However, a substantial proportion of patients have persisting neurocognitive impairment beyond six months.

NOTES

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Table 1: Glasgow outcome scale (GOS) and extended Glasgow outcome scale (GOSE).

GOS	GOSE	Definition
1=Dead	1=Dead	Dead
2=Vegetative state	2= Vegetative state	Unresponsive and speechless
3=Severe disability	3= Lower severe disability	Needs full assistance in ADL
	4= Upper severe disability	Needs partial assistance in ADL
4=Moderate disability	5=Lower moderate disability	Independent, but cannot resume work/school or all previous social activities
	6=Upper moderate disability	Some disability exists, but can partially resume work or previous activities
5= Good recovery	7=Lower good recovery	Minor physical or mental deficits that affect daily life
	8= Upper good recovery	Full recovery or minor symptoms that do not affect daily life

Abbreviation: ADL, Activity of daily living

Table 2: Baseline demographics and clinical characteristics of 205 adult cases diagnosed with Herpes simplex virus 2 meningitis at Danish departments of infectious diseases from 2015 through 2020.

	Number of observations	N (%) or median (IQR)
Age (year)	205	35 (27-49)
Sex (female)	205	156 (76)
Predisposing conditions		
History of genital herpes	175	83 (47)
Previous viral meningitis	205	63 (31)
Immuno-compromised*	205	19 (9)
Pre-existing physical or cognitive deficits	205	26 (13)
Clinical presentation at admission		
Duration of symptoms (days)	203	1 (1-3)
Prodromal upper airways diseases	186	24 (13)
Prodromal gastrointestinal diseases	186	17 (9)
Headache	204	195 (95)
Neck stiffness	196	106 (54)
Nausea and/or vomiting	200	145 (73)
Photo- or phonophobia	188	143 (76)
Genital mucocutaneous lesions	193	15 (8)
History of fever	183	135 (74)
Temperature (Celsius)	199	37.8 (37.1-38.4)
Glasgow Coma Scale Score	201	15 (15-15)
Blood samples		
C-reactive protein (mg/L)	194	3 (1-6)
Blood culture performed	205	159 (78)
Blood culture positive	159	3 (2)**
Cerebrospinal fluid		
Time to lumbar puncture (hours)	205	2.0 (1.0-4.8)
Leukocytes (10^6/L)	205	360 (166-670)
Mononuclear leukocytes (10^6/L)	199	342 (147-620)
Percentage mononuclear leucocytes (%)	199	97 (91-99)
Protein (g/L)	200	1.1 (0.8-1.5)
CSF:plasma glucose ratio	132	0.52 (0.45-0.59)
Lactate (mmol/L)	120	3.1 (2.6-3.9)
Diagnosis established by (hierarchical order)		
Positive PCR of CSF	205	180 (88)
Positive intrathecal HSV antibody ratio	205	13 (6)

PCR of genital lesion and CSF pleocytosis	205	9 (4)
Previous confirmed HSV-2 meningitis***	205	3 (1)
Brain imaging during admission	205	90 (44)
Computed tomography (CT)	205	72 (35)
Magnetic resonance imaging (MRI)	205	32 (16)
Both CT and MRI	205	14 (7)
Brain imaging before lumbar puncture	205	61 (30)
Treatment		
Acyclovir or valacyclovir treatment	205	197 (96)*****
Time to antiviral treatment (hours)	181	4.9 (2.3-11.8)
Intravenous followed by oral antiviral treatment	197	145 (74)
Only intravenous acyclovir	197	20 (10)
Only valacyclovir	197	32 (16)
Total duration of antiviral treatment (days)	169	10 (7-14)
Empiric antibiotics for bacterial meningitis	204	113 (55)
Empiric dexamethasone for bacterial meningitis	204	93 (46)

*Immunocompromising conditions included: Diabetes mellitus (n=6), immunosuppressive medication (n=3), HIV (n=4), intravenous substance abuse (n=2), alcohol abuse (n=3), solid cancer (n=1), and hematological cancer (n=2). **Three were culture positive for skin flora bacteria and considered as contaminant without clinical relevance. ***No pathogen detected during the current episode of viral meningitis combined with previously documented HSV-2 meningitis. *****Antiviral treatment was not administered by doctors in these patients because they were only mildly symptomatic and already rapidly improving or discharged at time of microbiological diagnosis.

Table 3: Outcome of 205 adult cases diagnosed with Herpes simplex virus 2 meningitis at Danish departments of infectious diseases from 2015 through 2020.

	Time of outcome assessment, n/N (%)			
	Discharge	**1 month**	**3 months**	**6 months**
Glasgow Outcome Scale (GOS)				
1 Dead	0	0	0	0
2 Vegetative state	0	0	0	0
3 Severe disability	1/205 (0.5)	1/197 (0.5)	1/192 (0.5)	1/181 (0.6)
4 Moderate disability	62/205 (30)	43/197 (22)	35/192 (18)	18/181 (10)
5 Good recovery	142/205 (69)	153/197 (78)	156/192 (81)	162/181 (90)
Extended Glasgow Outcome Scale (E-GOS)				
1 Dead	0	0	0	0
2 Vegetative state	0	0	0	0
3 Lower severe disability	1/197 (0.5)	1/190 (0.5)	1/183 (0.6)	1/178 (0.6)
4 Upper severe disability	0	0	0	0
5 Lower moderate disability	23/197 (12)	10/190 (5)	6/183 (3)	3/178 (2)
6 Upper moderate disability	33/197 (17)	29/190 (15)	20/183 (11)	8/178 (4)
7 Lower good recovery	72/197 (37)	74/190 (39)	65/183 (36)	65/178 (37)
8 Upper good recovery	68/197 (35)	76/190 (40)	91/183 (50)	101/178 (57)

Table 4: Stratified and adjusted analyses of prognostic factors for unfavorable outcome (Glasgow Outcome Scale 1-4) among 205 adult cases diagnosed with Herpes simplex virus 2 meningitis at Danish departments of infectious diseases.

	Unfavorable outcome, n/N (%)			
Stratified analyses	**Discharge**	**1 month**	**3 months**	**6 months**
Sex				
Male	14/49 (29)	11/46 (24)	9/45 (20)	5/42 (12)
Female	50/156 (32)	33/151 (22)	27/147 (18)	14/139 (10)
Age (years)				
<35	27/101 (27)	18/95 (19)	15/91 (16)	8/87 (9)
≥35	37/104 (36)	26/102 (25)	21/101 (21)	11/94 (12)
Previous viral meningitis				
No	43/141 (31)	35/137 (26)	30/132 (23)	16/122 (13)
Yes	20/63 (32)	8/59 (14)	5/59 (8)	2/58 (3)
Immuno-compromise*				
No	57/186 (31)	39/179 (22)	32/175 (18)	15/164 (9)
Yes	7/19 (37)	5/18 (28)	4/17 (24)	4/17 (24)
Pre-existing physical or cognitive deficits				
None	56/179 (31)	38/172 (22)	30/167 (18)	14/156 (9)
Mild/moderate	8/26 (31)	6/25 (24)	6/25 (24)	5/25 (20)
Duration of symptoms (days)				
0-1	32/102 (31)	17/98 (17)	12/95 (13)	8/93 (9)
2-3	10/56 (18)	8/53 (15)	5/51 (10)	1/49 (2)
4-5	9/18 (50)	7/18 (39)	7/18 (39)	2/13 (15)
≥6	13/27 (48)	12/26 (46)	12/26 (46)	8/24 (33)
CSF leukocytes (10^6/L)				
0-99	10/28 (36)	8/28 (29)	8/28 (29)	5/25 (20)
100-499	34/101 (34)	22/96 (23)	16/92 (17)	6/86 (7)
500-999	14/53 (26)	9/52 (17)	6/50 (12)	4/48 (8)
≥1000	6/23 (26)	5/21 (24)	6/22 (27)	4/22 (18)
Treatment				
No antiviral treatment	1/8 (13)	0/8 (0)	0/8 (0)	0/8 (0)
Intravenous treatment exclusively	6/20 (30)	6/20 (30)	6/20 (30)	4/18 (22)
Oral treatment exclusively	6/32 (19)	5/32 (16)	3/31 (10)	2/30 (7)
Intravenous and oral treatment***	50/144 (35)	32/136 (24)	26/132 (20)	12/124 (10)
Antiviral treatment duration (days)				

1-10	34/111 (31)	24/104 (23)	17/100 (17)	8/94 (9)
≥11	20/58 (34)	13/57 (23)	12/56 (21)	6/53 (11)

Modified Poisson regression	**Crude relative risk (95% CI)**	**Adjusted relative risk (95% CI)****
Sex		
Male	Ref	Ref
Female	1.12 (0.68-1.85)	1.08 (0.65-1.79)
Age (years)		
<35	Ref	Ref
≥35	1.33 (0.88-2.01)	1.28 (0.83-1.97)
Immuno-compromise*		
No	Ref	Ref
Yes	1.20 (0.64-2.25)	1.07 (0.57-2.03)
CSF leukocytes (10^6/L)		
0-99	Ref	Ref
100-499	0.94 (0.53-1.66)	1.00 (0.56-1.77)
500-999	0.74 (0.38-1.45)	0.81 (0.41-1.62)
≥1000	0.73 (0.31-1.71)	0.78 (0.33-1.84)

CSF: Cerebrospinal fluid. 95% CI: 95% confidence interval. *Immunocompromising conditions included: Diabetes mellitus (n=6), immunosuppressive medication (n=3), HIV (n=4), intravenous substance abuse (n=2), alcohol abuse (n=3), solid cancer (n=1), and hematological cancer (n=2). **Adjusted for sex, age, immuno-compromise, and CSF leukocytes count. ***Median duration of intravenous acyclovir was 3 days (IQR 1-4).

FIGURE LEGEND

Figure 1: Age distribution stratified by immune status among 205 adult cases hospitalized with HSV-2 meningitis at departments of infectious diseases in Denmark from 2015 through 2020.