



## Short Communication

Viral infections of the central nervous system in elderly patients: a retrospective study<sup>☆</sup>

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## SUMMARY

**Objectives:** Very few data exist on viral meningitis and encephalitis in elderly patients (>65 years old). **Methods:** This study investigated the detection of herpes simplex virus (HSV), varicella zoster virus (VZV), human herpes virus 6 (HHV-6), HHV-7, HHV-8, cytomegalovirus (CMV), Epstein–Barr virus (EBV), enterovirus (EV), human adenovirus (HAdV), human parechoviruses (HPeVs), and tick-borne encephalitis virus (TBEV) through real-time PCR (RT-PCR) in patients >65 years old who had cerebrospinal fluid (CSF) tested for a suspected central nervous system infection.

**Results:** A total of 2868 RT-PCRs were performed on 502 CSF samples. Overall, 65 positive RT-PCRs were found: 23 for HSV (35.4% of positives), 15 for EV (23.1% of positives), 14 for EBV (21.5% of positives), 12 for VZV (18.5% of positives), and one for CMV (1.5% of positives). A positive RT-PCR in CSF was detected in 24 (17.4%) patients aged ≥80 years and in 35 (9.6%) patients aged 65–79 years ( $p = 0.02$ ). VZV was more frequently detected in the oldest subjects (5.9% vs. 1.6%,  $p = 0.03$ ).

**Conclusions:** HSV was the most common viral aetiology identified in the study, with VZV infection being recognized more frequently in those patients aged ≥80 years.

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## 1. Introduction

Elderly patients (age >65 years) have worse outcomes for community-acquired meningitis and encephalitis, but these patients are underrepresented in clinical reports and very few data are available for patients ≥80 years old.<sup>1–3</sup>

This retrospective study investigated the detection of herpes simplex virus (HSV), varicella zoster virus (VZV), human herpes virus 6 (HHV-6), HHV-7, HHV-8, cytomegalovirus (CMV), Epstein–Barr virus (EBV), enterovirus (EV), human adenovirus (HAdV),

human parechoviruses (HPeVs), and tick-borne encephalitis virus (TBEV) through molecular techniques in patients aged >65 years who had cerebrospinal fluid (CSF) tested in routine clinical practice for a suspected central nervous system (CNS) infection.

## 2. Methods

All CSF samples tested for EV and/or HSV from August 1, 2012 to May 31, 2015 were included. The study was approved by the Ethics Committee for Clinical Experimentation, Padova Province (50443/08-21-15). Real-time PCRs (RT-PCRs) included in the diagnostic panel were done at the discretion of the treating physician and were performed using protocols currently applied at the Microbiology and Virology Unit of Padova Hospital.

Age was evaluated as a binary variable: 65–79 years vs. ≥80 years. The number of tests performed was reported as the median and 95% confidence interval (CI); the Mann–Whitney test, Chi-square test (with Yates' correction when appropriate), and Fisher's exact test were applied, as appropriate. The limit of significance for all analyses was established at  $p < 0.05$ .

<sup>☆</sup> SGP designed and coordinated the study, supervised the laboratory experiments, collected the data, interpreted the findings, and wrote the paper; MB performed the statistical analysis and wrote the paper; CDV performed the laboratory experiments; EF performed the laboratory experiments; SA performed the laboratory experiments and helped to interpret the findings; FDB performed the laboratory experiments; SP performed the laboratory experiments; MAB helped to interpret the findings; RM helped to interpret the findings; LB helped to interpret the findings; GP helped to interpret the findings and wrote the paper.

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**Table 1**  
Viral CSF RT-PCR results in 502 elderly patients with suspected meningitis and encephalitis

	Patients aged 65–79 years, n (%)	Patients aged ≥80 years, n (%)	p-Value	Total, n (%)
(A) RT-PCR performed in the two groups of patients, evaluated both as the absolute value and as the percentage with respect to the number of patients included in each age group. The viruses are listed according to the number of patients tested.				
HSV tested	358 (98.3)	138 (100)	0.12	496 (98.8)
VZV tested	308 (84.6)	118 (85.5)	0.8	426 (84.9)
CMV tested	262 (72)	92 (66.7)	0.24	354 (70.5)
EV tested	258 (70.9)	91 (65.9)	0.28	349 (69.5)
HPeVs tested	253 (69.5)	85 (61.6)	0.09	338 (67.3)
EBV tested	243 (66.7)	82 (59.4)	0.12	325 (64.7)
TBEV tested	107 (29.4)	30 (21.7)	0.08	137 (27.3)
HAdV tested	76 (20.9)	30 (21.7)	0.83	106 (21.1)
HHV-6 tested	100 (27.5)	39 (28.3)	0.86	139 (27.7)
HHV-7 tested <sup>a</sup>	72 (19.8)	28 (20.3)	0.89	100 (19.9)
HHV-8 tested	70 (19.2)	28 (20.3)	0.78	98 (19.5)
(B) Positive RT-PCR in the two groups of patients, evaluated both as the absolute value and as the percentage with respect to the number of tests performed for the specific virus (37 positive RT-PCRs for patients aged 65–79 years and 28 positive RT-PCRs for patients aged ≥80 years: total 65 positive RT-PCRs).				
HSV-positive	16 (4.5)	7 (5.1)	0.77	23 (4.6)
EV-positive	8 (3.1)	7 (7.7)	0.06	15 (4.3)
EBV-positive	8 (3.3)	6 (7.3)	0.12	14 (4.3)
VZV-positive	5 (1.6)	7 (5.9)	0.03 <sup>b</sup>	12 (2.8)
CMV-positive	0	1 (1.1)	0.09	1 (0.3)
HPeVs-positive	0	0	-	0
TBEV-positive	0	0	-	0
HAdV-positive	0	0	-	0
HHV-6-positive	0	0	-	0
HHV-7-positive	0	0	-	0
HHV-8-positive	0	0	-	0

CSF, cerebrospinal fluid; RT-PCR, real-time polymerase chain reaction; HSV, herpes simplex virus; VZV, varicella zoster virus; CMV, cytomegalovirus; EV, enterovirus; HPeVs, human parechoviruses; EBV, Epstein–Barr virus; TBEV, tick-borne encephalitis virus; HAdV, human adenovirus; HHV, human herpes virus.

<sup>a</sup> HHV-7 tested from January 2013.

<sup>b</sup> Significant value.

### 3. Results

Five hundred and two CSF specimens were collected by lumbar puncture from August 2012 to the end of May 2015. A total of 2868 viral RT-PCRs were performed: 2107 in patients aged 65–79 years and 761 in patients aged ≥80 years.

The median number of tests was comparable in patients who showed viral detection (6, 95% CI 4–6) and in those who did not (5, 95% CI 4–6), and in patients aged 65–79 years (6, 95% CI 5–6) and aged ≥80 years (5, 95% CI 4–6). Female sex was more common in patients aged ≥80 years (male/female 64/74, 53.6% vs. male/female 220/144, 39.6% in younger patients;  $p = 0.006$ ), but no sex-related difference in positive results was found.

Overall, 65 positive RT-PCRs were detected: 23 for HSV (35.4% of positives; 20 HSV-1, one HSV-2, and two not typed), 15 for EV (23.1% of positives), 14 for EBV (21.5% of positives), 12 for VZV (18.5% of positives), and one for CMV (1.5% of positives) (Table 1).

The EBV DNA value was positive under the threshold level in 11 of the 14 positive patients; the other values found were 2301 copies/ml, 5000 copies/ml, and 7618 copies/ml.

Twenty-four patients aged ≥80 years (17.4%) were found to be RT-PCR-positive, a value significantly higher ( $p = 0.02$ ) with respect to the group of subjects aged 65–79 years (35 subjects, 9.6%). Of note, VZV was more frequently detected in the oldest subjects (5.9% vs. 1.6%;  $p = 0.03$ ).

### 4. Discussion

HSV was the most frequently detected agent and the percentage was comparable in patients aged 65–79 years and ≥80 years (4.5% and 5.1%, respectively). The overall percentage of EV and EBV positivity was similar to that of HSV, but subjects aged ≥80 years were twice as likely to have a positive test with respect to patients aged 65–79 years (7.7% vs. 3.1% for EV and 7.3% vs. 3.3% for EBV).

The data from the present study on patients aged ≥80 years are quite different from those reported by Kleines et al. in a study that investigated only HSV, VZV, EBV, CMV, HHV-6, and EV: they detected HSV in 3.1% of subjects, EBV in 1.1%, and no EV positivity.<sup>4</sup> The different results obtained for the detection of EV may be related to the different EV genotype or subgenotype.<sup>5</sup> Of note, only VZV showed an age-related significant difference: the positivity rate in patients aged ≥80 years was 5.9%, significantly higher than that reported in subjects aged 65–79 years (1.6%).

No HHV-6-, HHV-7-, HAdV-, or TBEV-positive RT-PCR was found in the patients studied. The involvement of these viruses in adult CNS disease is limited to rare cases, or almost exclusively limited to specific geographic areas (TBEV).<sup>3,6,7</sup> Moreover, the testing rate was very low (27.7%, 19.9%, 21.1%, and 27.3%, respectively).

Limitations of this study are the retrospective design and the absence of clinical data. Nevertheless, the large cohort, the number of the viruses tested, and the focus on patients aged ≥80 years represent clear strengths.

This study provides an updated picture of virus detection in elderly patients with a suspected CNS disease. HSV was the most frequently diagnosed, followed by EV, but VZV infection was found to be significantly more frequent in patients aged ≥80 years.

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