SUPPLEMENTARY DATA

Supplementary Table 1 Primers and probes used in this study

Name	Target	Sequence[a]
HSV-1 US4_Fw	Human herpesvirus 1 *US4*	TCCTSGTTCCTMACKGCCTCCC
HSV-1 US4_Rv	Human herpesvirus 1 *US4*	CGTCTGGACCAACCGCCACACAGGT
HSV-1 US4_probe	Human herpesvirus 1 *US4*	*FAM*-GCAGICAYACGTAACGCACGCT-*BHQ1*
HSV-1 LAT_Fw	Human herpesvirus 1 *LAT*	CCCACGTACTCCAAGAAGGC
HSV-1 LAT_Rv	Human herpesvirus 1 *LAT*	AGACCCAAGCATAGAGAGCCAG
HSV-1 LAT_probe	Human herpesvirus 1 *LAT*	*FAM*-CCCACCCCGCCTGTGTTTTTGTG-*BHQ1*
VZV ORF38_Fw	Human herpesvirus 3 *ORF38*	AAGTTCCCCCCGTTCGC
VZV ORF38_Rv	Human herpesvirus 3 *ORF38*	CCGCAACAACTGCAGTATATATCGTCTCA
VZV ORF38_probe	Human herpesvirus 3 *ORF38*	*FAM*-TGGACTTGAAGATGAACTTAATGAAGC-*BHQ1*
HMBS_Fw	Homo sapiens *HMBS*	GCCTGCAGTTTGAAATCAGTG
HMBS_Rv	Homo sapiens *HMBS*	CGGGACGGGCTTTAGCTA
HMBS_probe	Homo sapiens *HMBS*	*FAM*-CGCAGGCACTCGTACTGCTCGCT-*BHQ1*
ApoE2_Fw	Homo sapiens *APOE2*	GCGGACATGGAGGACGTGT
ApoE2_Rv	Homo sapiens *APOE2*	CCTGGTACACTGCCAGGCA
ApoE3_Fw	Homo sapiens *APOE3*	CGGACATGGAGGACGTGT
ApoE3_Rv	Homo sapiens *APOE3*	CTGGTACACTGCCAGGCG
ApoE4_Fw	Homo sapiens *APOE4*	CGGACATGGAGGACGTGC
ApoE4_Rv	Homo sapiens *APOE4*	CTGGTACACTGCCAGGCG
ApoE_Probe	Homo sapiens *APOE*	*FAM*-CAGCTCCTCGGTGCTCTGGC-*BHQ1*
ApoE_seq1	Homo sapiens *APOE*	AGCCCTTCTCCCCGCCTCCCACTGT
ApoE_seq2	Homo sapiens *APOE*	CTCCGCCACCTGCTCCTTCACCTCG

[a]5' and 3'-modifications of TaqMan probes are indicated. *FAM* 6-Carboxyfluorescein, *BHQ1* black hole quencher 1

Supplementary Table 2 FFPE TG samples used in this study

Subject	Age[a]	Gender[b]	PMI[c]	Cause of death	Neurological disease	HSV-1 status[d]
1	81	F	3:35	Cachexia and dehydration	Alzheimer's disease	negative
2	82	F	5:55	Cardiac arrest	Alzheimer's disease	negative
3	89	F	4:30	Peritonitis	Alzheimer's disease	positive
4	87	F	8:10	Uremia by dehydration	Alzheimer's disease	positive
5	86	F	5:15	Cachexia and dehydration	Alzheimer's disease	positive
6	81	M	8:21	Euthanasia	Parkinson's disease	positive
7	62	F	12:35	Cachexia with pulmonary insufficiency	Multiple sclerosis	positive
8	80	F	9:30	Cardiac arrest	Bipolar disorder	positive
9	103	F	6:35	Dehydration and pneumonia	Tauopathy	positive
10	89	M	6:50	Urosepsis	non-demented control	positive

[a]Age in years; [b]F, female; M, male; [c]PMI, post-mortem interval; [d]HSV-1 infection status based on serology and HSV-1 LAT ISH

Supplementary Table 3 TBI patients used in this study

Subject	Age[a]	Gender[b]	Interval TBI – death
1	84	M	0 days (acute)
2	48	M	7 days
3	13	F	11

[a]Age in years; [b]F, female; M, male

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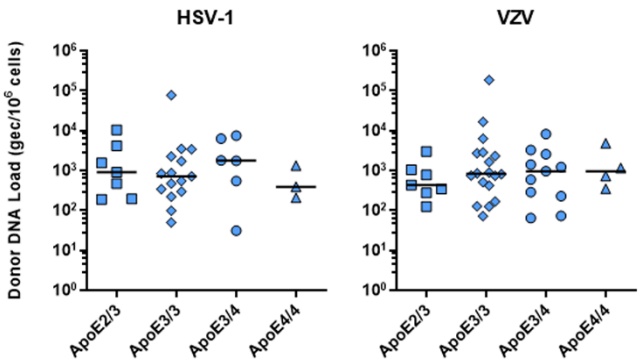
Supplementary Table 4 FFPE AD samples used in this study

Subject	Age[a]	Gender[b]	PMI[c]	Cause of death	Neurological disease	HSV status[d]
1	88	M	4:40	Cachexia and dehydration	Alzheimer's disease	positive
2	74	M	8:00	Dehydration by possible cystitis	Alzheimer's disease	positive
3	86	M	05:10	Cachexia and dehydration	Alzheimer's disease	positive

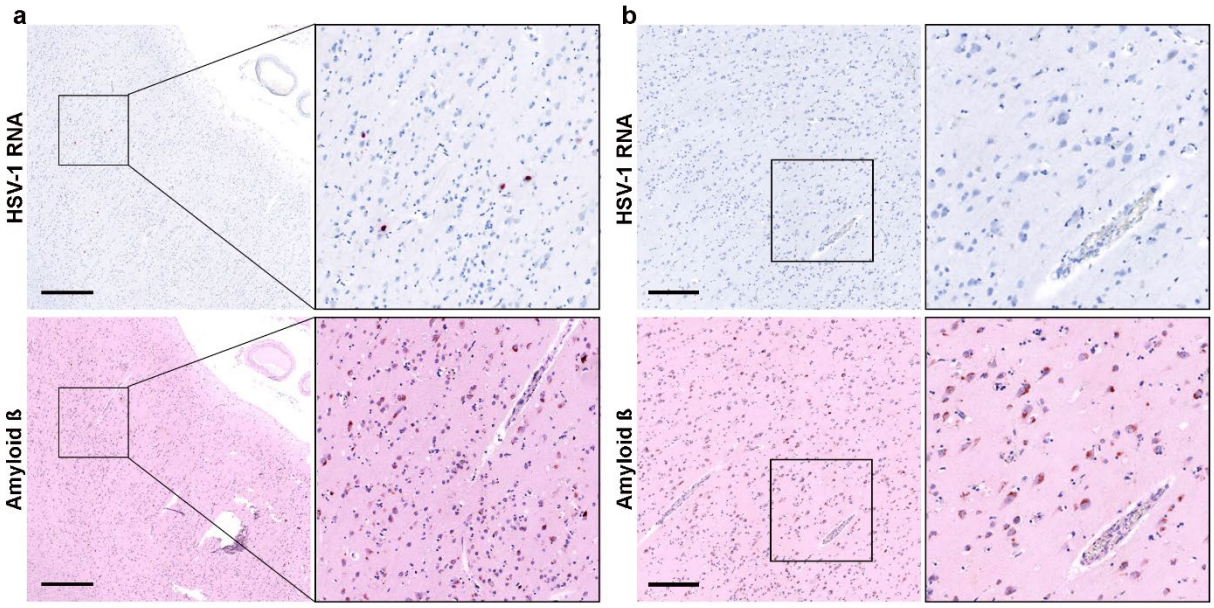
[a]Age in years; [b]F, female; M, male; [c]PMI, post-mortem interval; [d]HSV infection status based on HSV-specific IgG serology data

SUPPLEMENTARY FIGURE 1



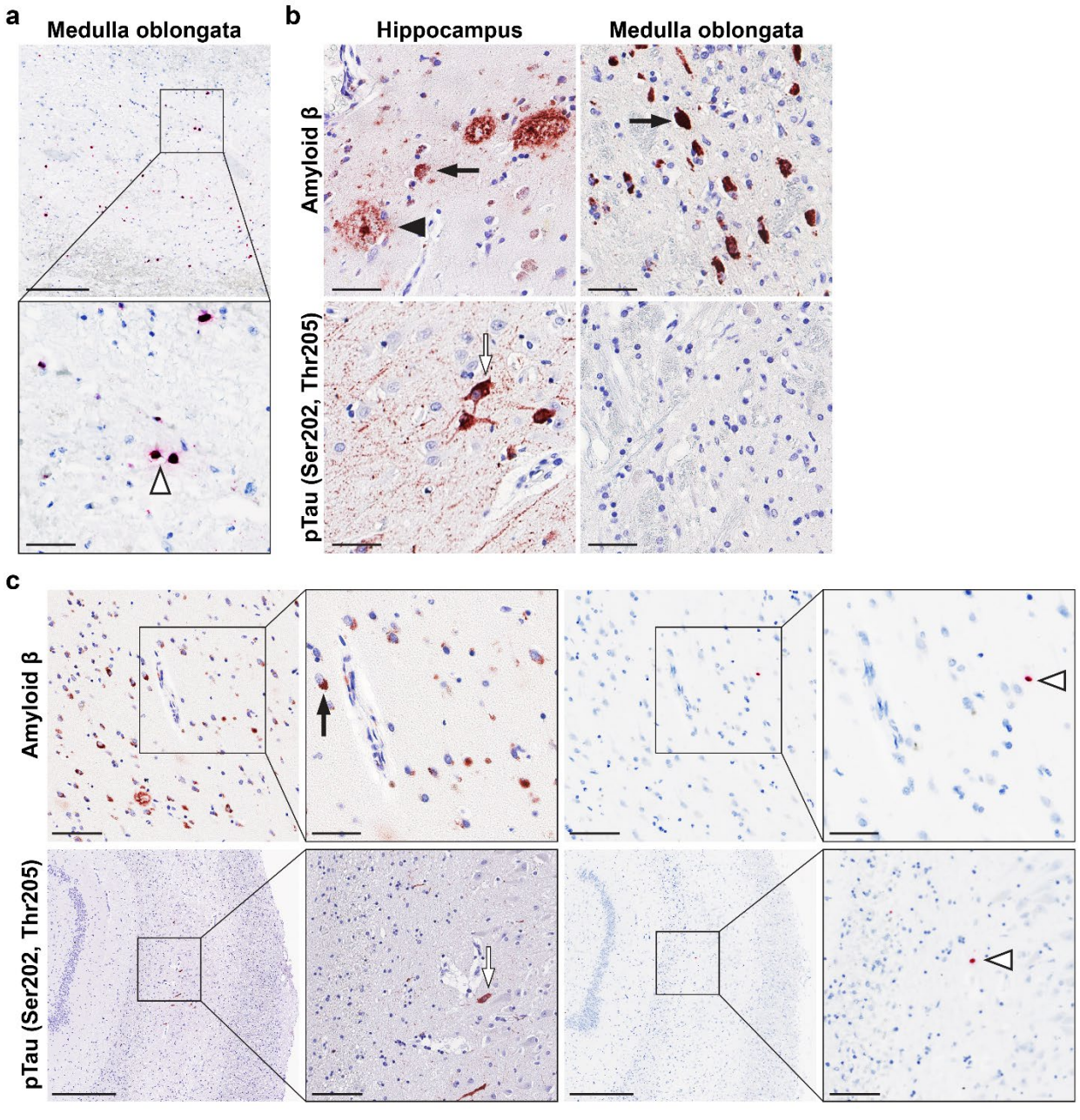
Supplementary Fig. 1 Quantification of latent HSV-1 and VZV DNA load in human TG stratified on *APOE* genotype. HSV-1- and VZV-specific qPCR and *APOE* genotyping was performed on DNA extracted from the trigeminal ganglia (TG) of AD patients and controls.

SUPPLEMENTARY FIGURE 2



Supplementary Fig. 2 Intraneuronal accumulation of Aβ protein is not restricted to areas of HSV-1 infection in brains of HSE patients. Consecutive slides were stained for HSV-1 RNA by ISH and Aβ by IHC. Aβ can be seen in areas with HSV-1 RNA (**a**) and in areas without HSV-1 RNA (**b**). Data shown for HSE donor 5. Scale bar: 500 µm (**a**) and 250 µm (**b**).

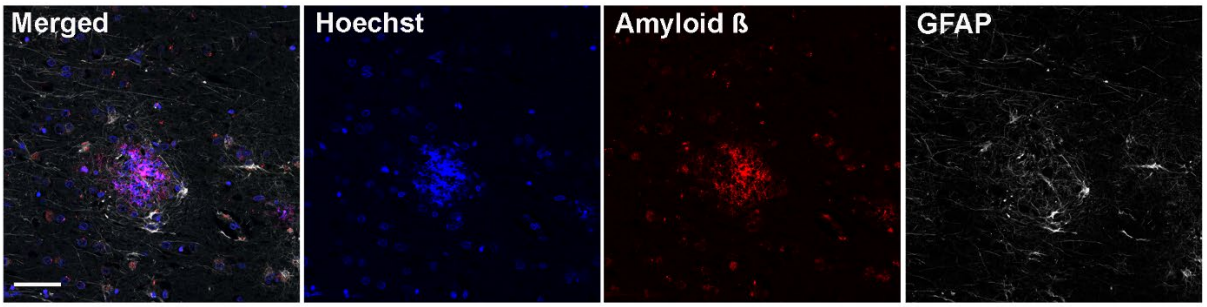
SUPPLEMENTARY FIGURE 3



Supplementary Fig. 3 Lytic VZV infection is not associated with Aβ plaques or NFT in brain of a VZV encephalitis patient. **a** Brain section stained for VZV RNA by ISH. Box indicates area shown at higher magnification. Open arrowhead indicates examples of VZV RNA-expressing cells. Scale bars indicate 250 μm (top) and 50 μm (bottom). **b** Brain

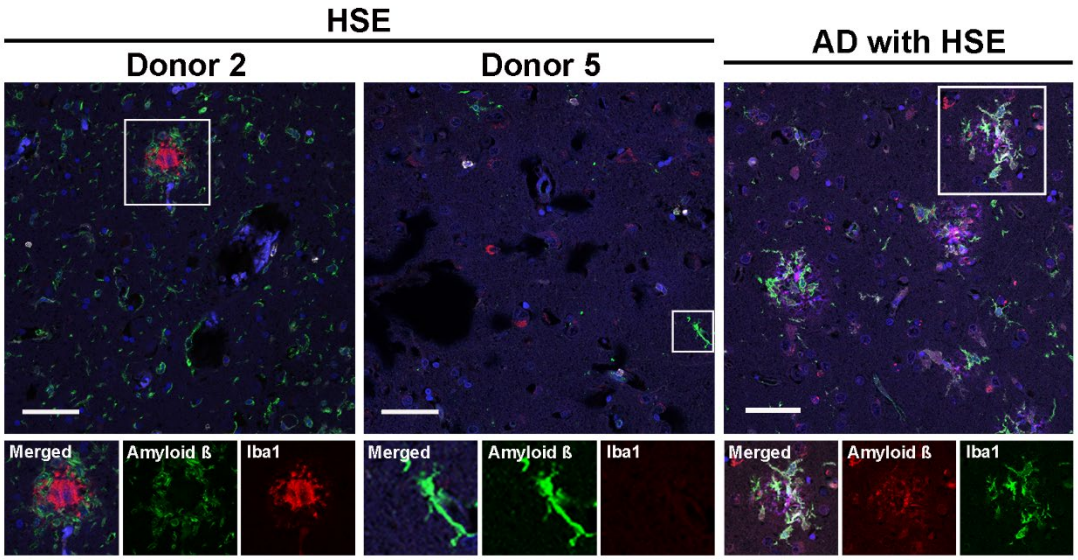
sections IHC stained for Aβ and pTau (Ser^{202}/Thr^{205}). Scale bars indicate 50 μm. **c** Consecutive brain sections were IHC stained for Aβ and pTau (Ser^{202}/Thr^{205}) or stained for HSV-1 RNA by ISH. Boxes indicate areas shown at higher magnification. Filled arrow indicates intracellular Aβ protein, open arrow indicates NFT and open arrowhead indicates VZV RNA-expressing cells. Scale bars indicate 50 μm (Aβ, high magnification), 100 μm (Aβ, low magnification; pTau high magnification) and 500 μm (pTau, low magnification).

SUPPLEMENTARY FIGURE 4



Supplementary Fig. 4 Prominent GFAP staining of astrocytes interacting with Aβ plaques brain of an AD patient with concurrent HSE. IF staining for Aβ (red), GFAP (white) and nuclei (Hoechst-33342; blue). Scale bar: 50 µm.

SUPPLEMENTARY FIGURE 5



Supplementary Fig. 5 Microglia morphology and density in the brain of HSE patients and AD patient with HSE. Brain tissue sections were IF stained for Aβ (red), Iba1 (green) and nuclei (Hoechst-33342; blue). Boxes indicate areas shown at higher magnification. Scale bar: 50 μm.