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**Latency of Herpes simplex virus type-1 in human geniculate and vestibular ganglia is associated with infiltration of CD8+ T-cells**

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5 associated with infiltration of CD8+ T-cells  
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3 Abstract  
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6 Herpes simplex virus type-1 latency and CD8+ T-cell occurrence were investigated in  
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8 the trigeminal, geniculate, and vestibular ganglia from seven deceased humans. The  
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10 HSV-1 "latency-associated transcript" was assessed by in situ-hybridization and  
11  
12 quantitative RT-PCR. Infiltration of CD8+ T-cell was detected by  
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14 immunohistochemistry and quantitative RT-PCR.  
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17 The data show that HSV-1 latency and CD8+ T-cell infiltration are not solely confined  
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19 to the trigeminal ganglia but can also occur in other cranial ganglia along the  
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21 neuroaxis. However, the HSV-1 latency transcripts in the geniculate and vestibular  
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23 ganglia were expressed at a very low level. The difference in CD8 transcript levels  
24  
25 among HSV-1 latently infected trigeminal ganglia, geniculate, and vestibular ganglia  
26  
27 was less conspicuous. Colocalisation of latent HSV-1 and CD8+ T-cells in geniculate  
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29 and vestibular ganglia supports further the hypothesis that HSV-1 reactivation is  
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31 possible in these ganglia and is the cause of Bell's palsy and vestibular neuritis.  
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39 Key words: cranial ganglia; qRT-PCR; LAT; CD8+ T-cells  
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## Introduction

Herpes virus simplex type-1 (HSV-1) has been linked to a variety of clinical syndromes of the nervous system. After primary infection of the epithelium (stomatitis aphtosa), HSV-1 enters the axon terminals and is carried by axonal transport to sensory neurons of the human cranial nerve ganglia, where it establishes lifelong latency. HSV-1 latency is characterized by restricted viral expression: an abundant expression of the latency-associated transcript (LAT) (Stevens et al., 1987) and very low amounts of immediate early (IE) genes (Kramer & Coen, 1995; Derfuss et al., 2007). Findings from the HSV-1 mouse model and from humans suggest that a chronic inflammation accompanies HSV-1 latency in the trigeminal ganglia (Shimeld et al., 1995; Theil et al., 2003). Previous investigations revealed that the highest frequency of neurons, that were positive for the latency-associated transcript, is found in the human trigeminal ganglia. However, latency-associated transcripts were also present, although in lower amounts in the geniculate and vestibular ganglia (Theil et al., 2001). Decreasing amounts of the latency-associated transcript from the trigeminal ganglia to the geniculate and vestibular ganglia are compatible with the hypothesis that HSV-1 migrates along the lingual nerve to the trigeminal and geniculate ganglia and via the facio-vestibular anastomoses to the vestibular ganglia (Arbusow et al., 1999). A large post-mortem study on human trigeminal ganglia demonstrated that latent HSV-1 is accompanied by an abundant CD8+ T-cell infiltration (Theil et al., 2003). According to the HSV-1 mouse model, one would expect that in all ganglia, where HSV-1 becomes latent, there should also be a T-cell infiltration, since this is supposed to maintain the virus in its latent state (Khanna et al., 2003). However, given that symptomatic HSV-1 reactivations from human trigeminal ganglia occur very frequently in humans (cold sores), the prominent T-cell

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3 infiltration is possibly a consequence of continuing asymptomatic or symptomatic  
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5 reactivations that are distinctive of the trigeminal ganglia.  
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8 The aim of the present study was to determine whether immune infiltration occurs in  
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10 other cranial ganglia (geniculate and vestibular ganglia), which are known to also  
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12 harbor latent HSV-1. An affirmative answer would indicate viral activity (e.g.,  
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14 symptomatic or asymptomatic reactivations). The presence of latency-associated  
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16 transcript and T-cells in the geniculate and vestibular ganglia would affirm the  
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18 hypothesis that HSV-1 reactivations are to be expected at this site and that they  
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20 cause neurological entities like Bell's palsy and vestibular neuritis.  
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## Material and Methods

The Ethics Committee of the Medical Faculty of the Ludwig-Maximilians University of Munich has approved the use of autopsy samples for the present study. The cause of death of the subjects included in the study was related to trauma. None had lesions suggestive of an active orolabial herpes infection. There were no records that they had suffered from vestibular neuritis or any other neurological disorder during their lifetime.

The trigeminal, geniculate, and vestibular ganglia from seven individuals (ages 5 weeks to 40 years) were collected (Table 1A). Ganglia were embedded in Tissue tek<sup>®</sup> compound (Sakura, Zoeterwoude, The Netherlands) and stored at -70°C until use. Frozen sections were made of 8- $\mu$ m thickness and mounted on positively charged slides (SuperFrost<sup>+</sup>/Plus<sup>®</sup>, Menzel, Braunschweig, Germany). In parallel a number of tissue sections were collected for RNA extraction. Beforehand, tissue sections from each ganglion were stained with hematoxylin and eosin for morphologic examination and the RNA quality of each ganglion was evaluated.

For immunohistochemistry frozen tissue sections were thawed, dried at 37°C for 15 min, fixed in acetone for 10 min, and then incubated overnight with mouse anti-CD8 antibody. Afterwards tissue sections were incubated for 30 min in biotinylated rabbit anti-mouse IgG antibody (1:500; DAKO, Hamburg, Germany). The sections were incubated with peroxidase-conjugated streptavidin (DAKO, Hamburg, Germany) for 30 min, followed by a final wash, and then incubated with diaminobenzidine (DAB) (DAKO, Hamburg, Germany) for up to 10 min. For in-situ hybridization the protocol used was described in detail in a previous work (Theil, et al., 2001). The ISH signal was visualized by incubation in nitroblue tetrazolium (NBT) and X-phosphate (BCIP 5-bromo-4-chloro-3-indolyl-phosphate) staining solution.

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3 RNA extraction and cDNA synthesis were performed using commercially available  
4 kits (miRNeasy Mini Kit, Qiagen, Hilden; high capacity cDNA reverse transcription kit,  
5 Applied Biosystems, Foster City, CA, USA) according to the manufacturers'  
6 protocols. To quantify latency-associated transcripts and CD8 transcripts QuantiTect  
7 SYBR<sup>®</sup> green RT-PCR (Qiagen) was used on a GeneAmp 5700 Sequence Detection  
8 System (Applied Biosystems). The results were normalized to the housekeeping  
9 gene beta-actin. Primer and PCR conditions were published previously (Theil et al.,  
10 2003; Naoe et al., 2002; Derfuss et al., 2007).

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12 The occurrence of latent HSV-1 and T-cell infiltration in the trigeminal ganglia from  
13 the subjects included in this study was assessed previously. HSV-1 latency was  
14 detected by in-situ hybridization and RT-PCR for the latency-associated transcript.  
15 Cytotoxic T-cells were detected by CD8 immunohistochemistry and quantitative RT-  
16 PCR (Theil et al., 2003).

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18 The trigeminal ganglia from one individual who showed strong positivity for the  
19 latency-associated transcript on in-situ hybridization and for T-cells on  
20 immunohistochemistry, and the trigeminal ganglia from another individual who was  
21 negative for the latency-associated transcript and T-cells were included as controls  
22 (references) for quantitation of the latency-associated transcripts and CD8 T-cells  
23 (Table 1 B).



## Results

Tissue sections and the RNA from all ganglia were checked beforehand for the presence of neurons in the section and for RNA integrity. Due to morphological artifacts and RNA degradation in some ganglia, measurement of CD8 transcripts was not possible in the ganglia from each side of the same individual. Latency-associated transcript and CD8 expression could however be assessed in at least one side of the trigeminal, geniculate, and vestibular ganglia of each individual (Table 1A).

Of the fourteen trigeminal ganglia tested by in situ hybridization or RT-PCR, 6 showed positivity for the latency-associated transcript with either method. None of the 10 geniculate and 11 vestibular ganglia showed a positive signal for the latency-associated transcript when tested by in situ hybridization, but expression of the latency-associated transcript was detected at low levels by quantitative RT-PCR in the 2 vestibular and 2 geniculate ganglia from one individual (Table 1 (A), subject 5). The transcripts levels in the control trigeminal ganglia were 1000x higher than in the geniculate and vestibular ganglia (Table 1, B).

Infiltration of CD8+ T-cells was detectable by immunohistochemistry only in the trigeminal ganglia (data published earlier) but not in the geniculate and vestibular ganglia (data not shown). By means of quantitative RT-PCR, CD8 transcripts were detectable in all tested trigeminal, geniculate, and vestibular ganglia. In the ganglia of three individuals the transcription levels of CD8 were clearly elevated (Table 1, subjects 5, 6 and 7). In these subjects the trigeminal ganglia were also positive for the latency-associated transcript, and in one subject (Table 1 A, subject 5) even the geniculate and vestibular ganglia were positive for the latency-associated transcript.

In the geniculate and vestibular ganglia, that were positive for the latency associated transcript, the CD8 transcript levels were analogous to the CD8 transcript level of the

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3 control trigeminal ganglia (Table 1B, control 1), although the latency-associated  
4 transcripts in the geniculate and vestibular ganglia were very low when compared to  
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6 the levels in the trigeminal ganglia (Table 1B, control 1).  
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## Discussion

In the present study it was shown that CD8<sup>+</sup> T-cells infiltrate human cranial ganglia other than the trigeminal ganglia. The CD8 transcript levels in the geniculate and vestibular ganglia that contained the latency-associated transcripts were comparable with the levels found in the trigeminal ganglia that were positive for the latency-associated transcripts. These findings emphasize that HSV-1 latency is associated with chronic inflammation not only in the human trigeminal ganglia where frequent HSV-1 reactivation occurs but also in other ganglia linked anatomically (geniculate and vestibular ganglia). This is of clinical relevance, since it supports the view that Bell's palsy and vestibular neuritis are caused by reactivation of HSV-1. Up till now only the surrogate marker for HSV-1 latency, the latency-associated transcript, could be demonstrated in the geniculate and vestibular ganglia (Furuta et al., 1992; Furuta et al., 1993; Theil et al., 2001). Additional detection of CD8 T-cells in the HSV-1 latently infected geniculate ganglia and vestibular ganglia means that persistently or intermittently low levels of lytic gene expression occur in some neurons, and full reactivation is suppressed by CD8<sup>+</sup> T-cells. However, for some unknown reason the protective role of CD8 T-cells can be abrogated and the virus then replicates, leading to a reactivating disease (e.g., Bell's palsy and vestibular neuritis).

Interestingly, the levels of CD8 transcripts in the geniculate and vestibular ganglia, which did not contain the latency-associated transcript but were obtained from subjects who showed positivity for the latency-associated transcript in the trigeminal ganglia, exceeded the values seen in the trigeminal, geniculate, and vestibular ganglia from individuals who had not had any HSV-1 infection. On the one hand, the elevated levels of CD8 in these ganglia could be due to a very low load of latent virus, which is below the sensitivity of the analytical method applied. On the other hand, the CD8<sup>+</sup> T-cells might become sequestered at this site after a primary HSV-1

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3 infection has been cleared. Even though it is generally accepted that immune cells  
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5 invade the trigeminal ganglia in the course of a primary infection and a certain CD8+  
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7 T-cell population persists thereafter in order to maintain the virus in a latent state by  
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9 constant expression of effector molecules such as granzyme B and IFN-gamma (Liu  
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11 et al., 2001; Bergstrom, 1973), T-cells could persist without depending on viral  
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13 antigen to provide equipment for a second encounter with the virus. As a matter of  
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15 fact, a recent study demonstrated that a unique memory T-cell pool remains resident  
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17 in the skin well after HSV-1 has been cleared (Gebhardt et al., 2009). This CD8+ T-  
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19 cell population does not seem to depend on ongoing viral gene expression, but  
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21 shows preferential protection from a subsequent infection with HSV-1.  
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23 Correspondingly, entrapment of CD8+ T-cells in the geniculate and vestibular ganglia  
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25 without latent HSV-1 could stem from a cleared HSV-1 acute infection that  
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27 encompassed all cranial ganglia or an anterograde infection during the course of  
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29 HSV-1 reactivation in the trigeminal ganglia (Theil et al., 2001). These cells probably  
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31 have the same protective capacity as those found in the skin of HSV-1 infected mice  
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33 (Gebhardt et al., 2009) and humans (Zhu et al., 2007) and consequently limit viral  
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35 spread to additional neurological structures.  
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Table 1 (A): Quantitation of CD8 transcripts in human trigeminal, geniculate and vestibular ganglia from subjects whose trigeminal ganglia were either LAT negative or LAT positive

# Subjects	Age	Site	CD8 transcript levels		
			Trigeminal Ganglia	Geniculate Ganglia	Vestibular Ganglia
TG(LAT+/-)					
1 (LAT-)	5 weeks	Right	n.d.	30.2	58.8
		Left	26.2	15.2	34.8
2 (LAT-)	1.5 mo	Right	n.d.	24.4	78.9
		Left	9.4	n.d.	71.2
3 (LAT-)	9.0 months	Right	99.2	104.0	115.0
		Left	n.d.	n.d.	50.8
4 (LAT-)	5 years	Right	134.5	79.8	88.6
		Left	n.d.	n.d.	n.d.
5 (LAT+)	8 years	Right	410.6	271.3*	229.9*
		Left	388.4	296.8*	147.5*
6 (LAT+)	40 years	Right	239.0	159.2	291.6
		Left	n.d.	166.9	n.d.
7 (LAT+)	37 years	Right	126.4	94.2	139.2
		Left	n.d.	n.d.	n.d.

n.d. = not determined; LAT = latency-associated transcript; TG = trigeminal ganglia  
 \*The geniculate and vestibular ganglia from only this individual were positive for LAT when tested by TaqMan PCR. The LAT transcript levels ranged between 1 to 70 copies.

Table 1 (B): Quantitation of CD8 and LAT transcripts in human trigeminal ganglia (control tissue)

# Subjects	Age	Site	Trigeminal Ganglia	
			CD8 transcript levels	LAT transcript levels
1	41 years	Right	219.7	1149.2
		Left	406.2	2406.2
2	62 years	Right	78.8	0
		Left	125.0	0

The transcript levels represent the relative transcript number of the gene of interest (CD8 and LAT) compared to the housekeeping gene beta-actin. CD8 transcript levels ranging from 15 to 150 were considered part of the constitutive expression.