

# Human immunoglobulin G levels of viruses and associated glioma risk

Sara Sjöström · Ulf Hjalmar · Per Juto · Göran Wadell ·  
Göran Hallmans · Anne Tjønneland · Jytte Halkjaer ·  
Jonas Manjer · Martin Almquist · Beatrice S. Melin

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**Abstract** Few consistent etiological factors have been identified for primary brain tumors. Inverse associations to asthma and low levels of varicella-zoster virus, immunoglobulin (Ig) levels in prevalent cases have indicted a role for the immune system in the development of glioma. Because samples from prevalent cases of glioma could be influenced by treatments such as steroids and chemotherapy, we investigated pre-diagnostic samples from three large Scandinavian cohorts. To test the hypothesis that immune response levels to these viruses are associated etiologically with glioma risk, we investigated pre-

diagnostic immunoglobulin levels for cytomegalovirus (CMV), varicella-zoster virus (VZV), adenovirus (Ad), and Epstein-Barr virus (EBV) including the nuclear antigen (EBNA1) using plasma samples from 197 cases of adult glioma and 394 controls collected from population-based cohorts in Sweden and Denmark. Low VZV IgG levels were marginally significantly more common in glioma cases than the controls (odds ratio (OR) = 0.68, 95% CI 0.41–1.13) for the fourth compared with the first quartile ( $p = 0.06$  for trend). These results were more prominent when analyzing cases with blood sampling at least 2 years before diagnosis (OR = 0.63, 95% CI 0.37–1.08) ( $p = 0.03$ ). No association with glioma risk was observed for CMV, EBV, and adenovirus.

S. Sjöström (✉) · B. S. Melin  
Department of Radiation Sciences, Oncology, Umeå University,  
90187 Umeå, Sweden  
e-mail: sara.sjostrom@onkologi.umu.se

U. Hjalmar  
Department of Clinical Sciences, Paediatrics, Umeå University,  
90187 Umeå, Sweden

P. Juto · G. Wadell  
Department of Clinical Microbiology, Umeå University,  
90187 Umeå, Sweden

G. Hallmans  
Department of Public Health and Clinical Medicine,  
Nutritional Research, Umeå University, 90187 Umeå, Sweden

A. Tjønneland · J. Halkjaer  
Institute of Cancer Epidemiology, Danish Cancer Society,  
2100 Copenhagen, Denmark

J. Manjer  
Department of Surgery, Malmö University Hospital,  
Malmö University, Malmö, Sweden

M. Almquist  
Department of Surgery, Lund University Hospital,  
Lund University, Lund, Sweden

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## Introduction

Gliomas are the most common primary malignant brain tumor. Although glioma treatment strategies—surgery, irradiation, and chemotherapy—have improved, the prognosis is still poor compared with many other human malignancies [1, 2]. Recently, the concomitant use of chemotherapy and irradiation and the use of the antiangiogenic treatment bevacizumab have improved prognosis [3]. As few etiological factors for glioma have been identified, few effective preventive strategies have been developed [4, 5]. The only confirmed risk factors are high dose of ionizing radiation and some rare hereditary predisposing conditions that are only found in less than 5% of all glioma cases [6, 7]. A familial aggregation of gliomas has been observed in several studies [8–10] and recently

five genes with low penetrance have been strongly associated with glioma risk [11, 12].

The question if viruses might cause, promote, or prevent human brain tumors is of great interest as viruses have been proven to cause several other types of cancers [13]. Earlier studies have shown evidence of viral DNA or proteins in tumor tissue for example JCV and SV40 [14, 15]. CMV and adenoviruses have also been reported to be present in brain tumor tissue [16–20]. It is, however, unclear whether their presence is due to the immunosuppressive environment in the tumor, making it a predilection site for viruses, or whether the presence of viruses in the tumor is due to an etiological impact.

Immunologic response to viral infections may be associated with the risk of developing glioma or glioblastoma [1]. Statistically significant inverse associations of adult glioma to both history of chickenpox and immunoglobulin G antibodies against varicella-zoster virus have been reported [21–23]. Patients with glioma and glioblastoma had levels of anti-varicella-zoster virus immunoglobulin G significantly lower than controls, indicating that the level of immune response to viruses may play a role in glioma induction or progression. Although some studies speculated whether the lowered IgG-levels preceded tumor diagnosis, this has not been clarified. Furthermore, several studies have shown an inverse association between occurrence of allergic diseases and brain tumors, a finding that indicates that the immune system function is important for glioma etiology [24–26]. In this study, we investigated the association between IgG levels of four viruses in pre-diagnostic samples and whether these levels were associated with glioma risk.

## Materials and methods

### Study population

This case–control study was based on 197 glioma cases and 394 controls from three cohorts: Northern Sweden Health and Disease Study—The Medical Biobank (NSHDS) (79 glioma

cases and 158 controls); the Malmö Diet and Cancer Study (MDCS) (45 glioma cases and 90 controls); and the Diet, Cancer, and Health cohort from Copenhagen (73 glioma cases and 146 controls). The controls were matched for age, sex, and cohort. The male/female distribution was 47.7%/52.3%, and the median ages at blood sampling were 55.4 years in cases and 55.3 in controls. Table 1 describes the cases and controls from the different cohorts. The diagnosis of glioma was identified through linkage to the local cancer registries. The registries have close to 100% coverage of cancer diagnoses since both clinicians and pathologists in Sweden and Denmark are legally obligated to report cancer diagnoses.

For the Swedish cases, we were able to receive classification of the tumors according to SNOMED (Systematized Nomenclature of Medicine). A total of 61 glioblastoma (SNOMED 94403), 8 astrocytoma grade 1–2 (SNOMED 94003, 94203, 94213), 32 astrocytoma grade 3 (SNOMED 94013), 14 oligodendroglioma (SNOMED 94503, 94513, 94603), 2 oligoastrocytoma (SNOMED 93823), and 5 malignant glioma (SNOMED 93803), were seen in the Swedish cases. SNOMED classification was not available on the cases from Copenhagen.

### Northern Sweden health and disease study

NSHDS is a population-based cohort consisting of blood samples and questionnaires from three subcohorts [27]: The Västerbotten Intervention Program (VIP); the Västerbotten Mammary Screening Program; and the Northern Sweden MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Project. By June 2006, the VIP cohort comprised 94,630 samples from 74,690 individuals. These individuals were asked to participate in a health study the year they turned 40, 50, and 60. Since 1995, blood samples were collected for the Mammary Screening Program and have been added to the VIP cohort. From 1997, repeated screening was started in the Mammography Screening Program in the age group 50–69. The MONICA project provided 11,000 random blood samples from 7,500 individuals ranging from 25 to 64 years old. All cohorts were population based and contained 166,000 randomly

**Table 1** Descriptive table showing the male/female ratio (numbers and percentages for cases shown, and percentages for controls are the same as for cases) and median age at blood sample for the whole cohort and each cohort

	All		NSHDS		Malmö		Copenhagen	
	Case	Control	Case	Control	Case	Control	Case	Control
All	197	394	79	158	45	90	73	146
Male	94 (47.7%)	188	33 (41.8%)	66	25 (55.6%)	50	36 (49.3%)	72
Female	103 (53.3%)	206	46 (58.2%)	92	20 (44.4%)	40	37 (50.7%)	74
Median age at blood sample	55.4	55.3	50.1	50.1	58.1	58.0	57.5	57.6

selected men and women and 278,000 sample occasions. Seventy-nine individuals were later diagnosed with a glioma [28].

### The Malmö Diet and Cancer Study

The Malmö Diet and Cancer Study (MDCS) is a population-based prospective cohort study. Between 1991 and 1996, men and women between the ages of 44 and 77 were recruited with the main goal to study the impact of diet on cancer incidence and mortality. In all, 28,098 blood samples were stored in a medical biological bank. Regular follow-up with the national registries of mortality and cancer was done, and 45 individuals from the cohort were later diagnosed with a glioma [29, 30].

### Diet, cancer, and health—Denmark

The Diet, Cancer, and Health study is a population-based prospective cohort study from Denmark where 80,996 men and 79,729 women were invited to participate between December 1993 and May 1997. The study included individuals between 50 and 64 years of age, born in Denmark, and with no diagnosis of cancer registered in the Danish Cancer Registry. Blood samples were obtained from 57,053 participants. From these individuals, 73 were later diagnosed with glioma [31].

The controls were collected from living individuals with no history of primary brain tumor at the time of case diagnosis and matched for age, gender, and calendar year of sampling. All individuals had a written informed consent and the study was approved by the local ethical committee at Umeå University.

### Laboratory methods

IgG antibodies for adenovirus, CMV, and VZV were analyzed, by in-house enzyme-linked immunosorbent assays (ELISA), at the Department of Virology at Umeå University. The origins of viral antigens used were for adenovirus a mixture of two local strains of Ad 3 and Ad 5, for CMV laboratory strain CMV 169 and for VZV a local strain. The analyses were blinded and performed in duplicate in a pair of wells coated with viral antigen and control antigen. In each run, high and low positive controls and negative controls were included. The sera were analyzed in a final dilution of 1/441, in which dilution there is a high correlation to antibody levels expressed as titers. The antibody activity in the single dilution of the sample was expressed in arbitrary units (AU), i.e., as a percentage of the net-absorbance (absorbance of virus-coated well) of the high positive control. Samples with <10 AU were negative. The IgG-anti-EBNA-1 response to EBV was measured using a

commercial ELISA from Biotest Germany according to the manufacturer's instructions. The antibody activity of the sample was expressed in AU as a percentage of the positive control and the manufacturer's cut-off value for presence of antibodies was used.

The IgG response to EBV viral capsid antigen (VCA) was analyzed by immunofluorescence assay in a high screening dilution (1/320) using butyric acid-stimulated P3HR1 lymphoma cells. The samples were blinded to case-control status and an experienced microscopist read all the samples (PJ). The fluorescence activity grading was aggregated to three categories: "low" (negative in 1/320 dilution), "intermediate" (weak positive), and "high" (intermediate and strong positive). Negative samples in 1/320 dilution were identified by re-analysis in 1/20 dilution. VCA was not used in the statistical analyses except for ruling out active infection. All methods are accredited at The Swedish Board for Accreditation and Conformity Assessment.

### Statistical methods

The proportions of cases and controls that were positive for the different immunoglobulin G and the mean age at blood sample in these groups were calculated and were estimated separately for glioma and for glioblastoma (SNOMED 94403). In the glioblastoma group, only the Swedish cases were available for analysis as the SNOMED code was not available for the Danish cases. The IgG antibody levels were divided into four same-sized quartiles, and cut-offs were based on IgG levels in controls. Binary logistic regression was used to compare the quartiles between cases and controls, and the lowest quartile was set as a reference. All odds ratios (OR) were adjusted for sex, cohort (Umeå, Malmö, and Denmark), and age at blood sampling. Separate analyses were also performed on cases with blood samples taken at least 2 years before diagnosis to omit any bias associated with the preclinical phase of the disease. The correlation between genotypes and IgG quartiles was performed by chi-square test using Fisher's exact test and  $p < 0.05$  was identified as the level for significance. SPSS software (v. 17) was used for the analyses.

### Results

Overall, there were high levels of seropositivity for the studied viruses, varying from 85.2 to 100%, and this result was similar in cases and controls (Table 2). The analyses were successful for close to 100% of the subsets of immunoglobulin. The mean age at blood samples did not differ significantly between the cases and the controls

**Table 2** Incidence of subjects positive for immunoglobulin G antibodies, in adenovirus, cytomegalovirus, Epstein-Barr virus, and varicella-zoster virus in the Umeå, Malmö, and Copenhagen cohorts

	All subjects		Controls		Glioma cases			Glioblastoma Sweden		
	No. positive/ total no.	Positive (%)	No. positive/ total no.	Positive (%)	No. positive/ total no.	% positive	<i>p</i> - value	No. positive/ total no.	% positive	<i>p</i> - value <sup>a</sup>
Immunoglobulin G antibodies										
Adenovirus	584/589	99.2	388/393	98.7	196/196	100	0.18	61/61	100	1.00
Cytomegalovirus	504/589	85.6	335/393	85.2	169/196	86.2	0.80	53/61	86.9	1.00
Epstein-Barr virus	511/587	87.1	347/391	88.7	164/196	83.7	0.09	54/61	88.5	0.15
Varicella-zoster virus	582/589	98.8	389/393	99.0	193/196	98.5	0.69	59/61	96.7	0.26

Cases/controls and Swedish cases (Umeå and Malmö) with glioblastoma shown separately. Information on tumor subtypes was not available for the cases from Copenhagen. No significant difference in numbers positive between cases and controls

<sup>a</sup> Controls from Copenhagen excluded in the analysis

**Table 3** Mean ages at blood sample for cases and controls from the Umeå, Malmö, and Copenhagen cohorts

	Positive		Negative	
	Mean age (years)	No. of Subjects	Mean age (years)	No. of Subjects
Immunoglobulin G antibodies				
Controls				
Adenovirus	54.7	389	58.7	5
Cytomegalovirus	54.8	336	54.6	58
Epstein-Barr virus <sup>a</sup>	54.6	347	56.7	44
Varicella-zoster virus	54.7	390	59.2	4
Cases				
Adenovirus	54.8	197		0
Cytomegalovirus	54.7	170	55.4	27
Epstein-Barr virus <sup>a</sup>	55.0	164	53.8	32
Varicella-zoster virus	54.7	194	60.3	3

Positive or negative for immunoglobulin G antibody levels for adenovirus, cytomegalovirus, Epstein-Barr virus, and varicella-zoster virus. There are no differences in mean age for cases and controls as the controls are matched to cases on age and year of blood sample

<sup>a</sup> Based on immunoglobulin G antibody levels analyzed using EBNA

(Table 3). The quartiles did not differ significantly between glioma and glioblastoma cases and controls, but a non-significant trend of lower VZV odds ratios was seen in the second, third, and fourth quartile (OR = 0.85, 95% CI 0.53–1.36; OR = 0.74, 95% CI 0.45–1.23; and OR = 0.68, 95% CI 0.41–1.13, respectively) ( $p = 0.06$ ) (Table 4). The trend test was significant when restricting the analyses to glioma cases with a latency of more than 2 years from sampling to glioma diagnosis (total 164 cases) (p-trend test,  $p = 0.03$ ) (Table 5).

## Discussion

To our knowledge, the present study is the first comprehensive study where virus-serology for EBV, CMV, VZV, and adenovirus is analyzed in samples from glioma/glioblastoma cases taken before diagnosis. This has previously been studied in astrocytoma for JC virus, BK virus, and simian virus 40, but no association to risk was found [32].

We found that immunoglobulin G to varicella-zoster virus was lower in cases versus controls especially in samples taken at least 2 years before diagnosis, a finding that indicates there might be an etiological association. No association between antibody levels for CMV, EBV, or adenoviruses and glioma risk was found.

Varicella-zoster virus (VZV) is neurotropic, and viruses remain permanent in neural ganglia after a primary infection. Furthermore, several studies have shown that immunoglobulin G levels of VZV are lower in serum from glioma cases, especially glioblastoma cases, compared with controls [21–23]. This lower level of VZV in serum from glioma cases could be because the tumor itself or the early treatment of the tumor influenced the immune response levels. Our data show a significant trend for lower VZV IgG levels especially in cases with blood samples taken more than 2 years before diagnosis, indicating that this could be a true etiological association. A medical history of asthma and allergies have been inversely correlated to glioma in several case–control studies indicating that the immune system may be a key player in glioma development [33, 34]. The biological reasons for this association are currently unknown. A previously stated theory is that a strong immune system more easily could detect viruses and therefore be able to inhibit the growth of small cancer cell clusters [22]. That can be demonstrated by the recent study showing that T-cell infiltration impacts on glioblastoma survival [35].

**Table 4** Cases and controls odds ratios (OR) and 95% confidence intervals (CI) for risk of glioma in the Umeå, Malmö, and Copenhagen cohorts and glioblastoma in the Umeå and Malmö cohorts

	Cases		Glioma cases versus controls		Glioblastoma cases		Glioblastoma cases versus controls <sup>b</sup>	
	No.	%	OR	(95% CI)	No.	%	OR	(95% CI)
Adenovirus, negative versus positive								
Adenovirus, quartiles								
1st	40	20.4	1.0		16	26.2	1.0	
2nd	59	30.1	1.39	(0.85–2.28)	16	26.2	0.81	(0.37–1.79)
3rd	42	21.4	1.07	(0.63–1.81)	15	24.6	0.95	(0.42–2.12)
4th	55	28.1	1.27	(0.76–2.12)	14	23.0	0.57	(0.25–1.31)
p-trend			0.49				0.28	
Cytomegalovirus, negative versus positive								
Cytomegalovirus, quartiles								
1st	48	24.5	1.0		15	24.6	1.0	
2nd	62	31.6	1.18	(0.73–1.90)	19	31.1	0.93	(0.42–2.05)
3rd	41	20.9	1.08	(0.85–1.38)	14	23.0	0.96	(0.65–1.43)
4th	45	23.0	1.06	(0.90–1.24)	13	21.3	0.98	(0.75–1.27)
p-trend			0.67				0.36	
Epstein-Barr virus <sup>a</sup> , negative versus positive								
Epstein-Barr virus <sup>a</sup> , quartiles								
1st	58	29.6	1.0		17	27.9	1.0	
2nd	46	23.5	0.79	(0.49–1.29)	15	24.6	0.76	(0.34–1.70)
3rd	43	21.9	0.71	(0.44–1.16)	16	26.2	0.71	(0.33–1.55)
4th	49	25.0	0.78	(0.49–1.26)	13	21.3	0.63	(0.28–1.44)
p-trend			0.25				0.17	
Varicella-zoster virus, negative versus positive								
Varicella-zoster virus, quartiles								
1st	55	28.1	1.0		12	19.7	1.0	
2nd	55	28.1	0.85	(0.53–1.36)	26	42.6	1.71	(0.78–3.74)
3rd	43	21.9	0.74	(0.45–1.23)	16	26.2	1.08	(0.45–2.57)
4th	43	21.9	0.68	(0.41–1.13)	7	11.5	0.39	(0.14–1.08)
p-trend			0.06				0.02	

All odds ratios are adjusted for cohort, sex, and age at blood sample

<sup>a</sup> Based on immunoglobulin G antibody levels analyzed using EBNA

<sup>b</sup> Glioblastoma cases from the Umeå and Malmö cohorts. Copenhagen cases and controls excluded

Of course, a confounder may explain this association in our study as well as in previous studies.

Many reports have been published concerning potentially oncogenic viruses, notably some herpes viruses such as human cytomegalovirus (HCMV), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and adenoviruses. Human cytomegalovirus (HCMV) is a ubiquitous herpes virus that is of particular interest and has long been suspected to play a role in the development of human cancers [36]. This virus has an affinity for glial cells and may possibly play an important role in glioma etiology. This affinity has been shown to influence glioma cells in several ways that might contribute to tumor progression, resulting in altered tumor cell properties such as reduced apoptosis,

increased cell invasion, telomerase activation, and enhanced angiogenesis [37, 38]. A study published in 2002 reported that human cytomegalovirus (HCMV) gene products and nucleic acids were present in all 27 glioma samples investigated but not in other brain tissue [39]. Recently, this finding has been confirmed by other research groups [17, 18]. Although a causal relationship between HCMV and human cancer has not been clearly proven, it is obvious that the virus may have a potential to promote oncogenesis or tumor progression in human cells.

Epstein-Barr-virus infections (EBV) have shown a clear association with human malignancies and some CNS tumors [40]. An increased risk for primary central nervous system lymphoma occurs in immunodeficient patients [41].

**Table 5** Cases and controls odds ratios (OR) and 95% confidence intervals (CI) for risk of glioma in the Umeå, Malmö, and Copenhagen cohorts and glioblastoma in the Umeå and Malmö cohorts

	Cases		Glioma cases versus controls		Glioblastoma cases		Glioblastoma cases versus controls <sup>b</sup>	
	No.	%	OR	(95% CI)	No.	%	OR	(95% CI)
Adenovirus, negative versus positive								
Adenovirus, quartiles								
1st	35	21.3	1.0		14	24.1	1.0	
2nd	44	26.8	1.15	(0.67–1.96)	16	27.6	0.94	(0.42–2.11)
3rd	38	23.2	1.12	(0.64–1.93)	14	24.1	1.01	(0.43–2.37)
4th	47	28.7	1.28	(0.75–2.19)	14	24.1	0.67	(0.28–1.58)
p-trend			0.40				0.71	
Cytomegalovirus, negative versus positive								
Cytomegalovirus, quartiles								
1st	39	23.8	1.0		15	25.9	1.0	
2nd	49	29.9	1.14	(0.68–1.91)	17	29.3	0.86	(0.38–1.92)
3rd	36	22.0	1.07	(0.83–1.38)	14	24.1	0.93	(0.62–1.39)
4th	40	24.4	1.05	(0.88–1.24)	12	20.7	0.95	(0.73–1.24)
p-trend			0.92				0.66	
Epstein-Barr virus <sup>a</sup> , negative versus positive								
Epstein-Barr virus <sup>a</sup> , quartiles								
1st	46	28.0	1.0		17	29.3	1.0	
2nd	42	25.6	0.90	(0.54–1.50)	15	25.9	0.76	(0.34–1.70)
3rd	36	22.0	0.78	(0.46–1.31)	14	24.1	0.63	(0.28–1.40)
4th	40	24.4	0.79	(0.47–1.32)	12	20.7	0.57	(0.24–1.32)
p-trend			0.27				0.35	
Varicella-zoster virus, negative versus positive								
Varicella-zoster virus, quartiles								
1st	48	29.3	1.0		12	20.7	1.0	
2nd	47	28.7	0.84	(0.51–1.37)	24	41.4	1.59	(0.72–3.50)
3rd	35	21.3	0.70	(0.41–1.19)	15	25.9	1.03	(0.43–2.47)
4th	34	20.7	0.63	(0.37–1.08)	7	12.1	0.39	(0.14–1.08)
p-trend			0.029				0.031	

Only cases with at least 2 years between blood sample and glioma/glioblastoma diagnosis included. All odds ratios are adjusted for cohort, sex, and age at blood sample

<sup>a</sup> Based on immunoglobulin G antibody levels analyzed using EBNA

<sup>b</sup> Glioblastoma cases from the Umeå and Malmö cohorts. Copenhagen cases and controls excluded

EBV might be involved in pathogenesis of other brain tumors, i.e., glioma. There is, however, no conclusive evidence of any glial tumor associated with EBV infections [42, 43]. Adenovirus has been shown to be neurotropic and one study has shown it to be present in childhood brain tumors [20]. We did not find any evidence of an association of EBV or adenovirus immunoglobulin levels with glioma risk.

As the blood samples were taken before diagnosis, antibody levels were not affected by any anti-tumor therapy, an important difference compared with previous studies. These viral infections are common in the general population and the seroprevalences in cases and controls

were high, limiting the statistical power of this study. Larger nested case-control studies within cohorts—using both pre-diagnostic and post-diagnostic serological samples in combination with matched tumor sample to discern potential effects on antibody levels by tumor tissue or treatment effects—could provide valuable information. In conclusion, the present study indicates that immune response to the varicella-zoster virus might be associated with glioma risk.

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