

RESEARCH ARTICLE

Elevated Serum IL-17A but not IL-6 in Glioma Versus Meningioma and Schwannoma

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Abstract

Background: There is a Th1/Th2 cytokine imbalance and expression of IL-17 in patients with brain tumours. We aimed to compare the levels of IL-17A and IL-6 in sera of glioma, meningioma and schwannoma patients as well as in healthy individuals. **Materials and Methods:** IL-17A and IL-6 levels were measured in sera of 38 glioma, 24 meningioma and 18 schwannoma patients for comparison with 26 healthy controls by commercial ELISA assays. **Results:** We observed an increase in the IL-17A in 30% of glioma patients while only 4% and 5.5% of meningioma and schwannoma patients and none of the healthy controls showed elevated IL-17A in their sera (0.29 ± 0.54 , 0.03 ± 0.15 and 0.16 ± 0.68 vs. 0.00 ± 0.00 pg/ml; $p=0.01$, $p=0.01$ and $p=0.001$, respectively). There was also a significant decrease in the level of IL-6 in glioma patients compared to healthy controls (2.34 ± 4.35 vs. 4.67 ± 4.32 pg/ml; $p=0.01$). There was a direct correlation between the level of IL-17A and age in glioma patients ($p=0.005$). Glioma patients over 30 years of age had higher IL-17A and lower IL-6 in their sera compared to the young patients. In addition, a non-significant grade-specific inverse trend between IL-17A and IL-6 was observed in glioma patients, where high-grade gliomas had higher IL-17A and lower IL-6. **Conclusions:** Our data suggest a Th17 mediated inflammatory response in the pathogenesis of glioma. Moreover, tuning of IL-6 and IL-17A inflammatory cytokines occurs during progression of glioma. IL-17A may be a potential biomarker and/or immunotherapeutic target in glioma cases.

Keywords: Glioma - meningioma - schwannoma - IL-17A - IL-6 - serum

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Introduction

Gliomas and meningiomas comprise more than 70% of the primary brain tumors (Norden, et al., 2011). Gliomas are rare malignant tumors of Central Nervous System (CNS) with a higher prevalence among men (Bondy et al., 2008; Jiang and Uhrbom, 2012). Different names have been used to describe these heterogeneous tumors since the first classification in 1926, some of which are no longer in use (MacKenzie, 1926; Martin-Villalba et al., 2008). Astrocytomas were originally named based on their resemblance to Astrocytes. Astrocytomas are further subcategorized to four types based on the WHO classification and grade of the tumor (Jiang and Uhrbom, 2012). The most aggressive forms of gliomas are called glioblastoma (GBM) and are categorized as grade IV Astrocytomas (Jiang and Uhrbom, 2012). Meningiomas are the second most prevalent primary neoplasm of the CNS, which arise from the arachnoid cap cells of the arachnoid villi in the meninges (Kujas, 1993; Wiemels et al., 2010). The majority of these tumors are benign; however, in some cases these tumors can metastasize and become aggressive (Pfisterer et al., 2010). The diagnosis

of both types of brain tumors is originally based on pathological findings and different imaging methods including computed tomography (CT) scan, Magnetic resonance imaging (MRI), perfusion-weighted imaging (PWI), diffusion-weighted imaging (DWI), and Magnetic resonance spectroscopic imaging (MRSI) (Michaud et al., 2010; Norden, et al., 2011; Zhou et al., 2011; Jiang and Uhrbom, 2012). Schwannomas are also benign tumors originating from the Schwann cell sheath surrounding the nerves (Fong et al., 2011; Zhang et al., 2012).

The treatment of choice for gliomas is surgical removal of the tumor along with chemotherapy and radiotherapy (Kantelhardt et al., 2010; Pouratian and Schiff, 2010; Jiang and Uhrbom, 2012). However, surgery cannot be performed on most of the meningiomas due to the location of the tumor. In this case, the patient is usually followed up for the tumor progression and radiotherapy is also performed (Minniti et al., 2009; Wernicke et al., 2010). The difference in the aggressiveness of these 3 types of CNS tumors and the difference in the therapeutic approaches towards these cancers call for an extensive effort for finding new methods for their early diagnosis and/or follow-up.

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Biomarkers are of great value for diagnosis, grading, prognosis, and follow up of cancer patients. Serum has always been a good source of biomarkers, which can be obtained non-invasively. So far a number of serum biomarkers for glioma have been reported (Riemenschneider et al., 2010); however, none of the markers are approved for routine use for patients. A trend of increase in the number of inflammatory and immunological biomarkers including growth factors and cytokines have been observed over the past decade; some of which have been used in the treatment of cancer as well (Gutierrez and Schiff, 2011; Damasceno, 2011). Inflammation can promote malignant cell transformation, tumor growth and metastasis (Mantovani et al., 2008). Certain inflammatory cytokines are present at elevated concentrations in the blood circulation of patients with brain tumors and changes in their levels can be detected after radiotherapy (Gridley et al., 1998). The expression of IL-1 β , TNF- α and IL-6 genes in brain neoplasms and meningiomas is shown (Merlo et al., 1993). IL-6 is reported to induce STAT3 signaling in RT4 schwannoma cell line and plays a role in peripheral nerve regeneration (Lee et al., 2009). Denervated Schwann cells produce IL-6 and other chemotactic factors which may have an autocrine or paracrine action on the cells (Tofaris et al., 2002). On the other hand, both in vivo and in vitro production of IL-6 by glioblastoma cells is reported (Van Meir et al., 1990). A recent comprehensive study on potential biomarkers in glioblastoma has indicated IL-6 gene as the fourth highest expressed genes in glioblastoma with 1.3 fold increase of IL-6 protein in the sera of patients (Sreekanthreddy et al., 2010). In primary brain neoplasms, transcription of genes encoding for the inhibitory cytokines TGF- β and IL-10 is reported in more than 50% of samples. However, IL-6 transcripts could only be detected in malignant gliomas. Conversely, in brain metastases, no cytokine gene transcripts have been observed. Surprisingly, TGF- β transcripts were also detected in all meningiomas (Tofaris et al., 2002). Our understanding of the biology of primary CNS tumors will not only help in finding new biomarkers but will also lead to new therapeutic protocols.

The expression of another recently discovered proinflammatory cytokine, Interleukin-17A (IL-17A) has been found in various human tumors. IL-17 overexpression in tumor cell lines promotes angiogenesis and tumor growth when the tumors are implanted in immunodeficient mice, therefore suggesting a pro-tumor activity (Numasaki et al. 2003). In contrast, the expression of IL-17A in a hematopoietically-derived tumor was reported to promote tumor protection in immunocompetent hosts (Benchetrit et al., 2002). Therefore, the presence or absence of the adaptive immune system has been suggested to account for pro-or anti-tumor activities of IL-17A (Martin-Orozco et al., 2009).

IL-17 has been shown to be overexpressed in glioma tissues. This expression was shown to be accompanied by IL-6, IFN- γ , and IL-1 β without significant differences between grades of glioma (Hu et al., 2011). Interestingly, IL-6, G-CSF, and TNF- α are among the genes that are induced by IL-17 (Kryczek et al., 2007; Miyahara et al., 2008; Sfanos et al., 2008; Zhang et al., 2008). In a cohort

of primary brain tumors, an imbalance in the systemic IL-12/IL-10 balance as hallmarks of Th1/Th2 cytokine production has been shown. This Th1/Th2 cytokine imbalance in patients with brain tumors is similar to that observed in studies on several other tumor types (Kumar et al., 2006). Currently, it is not known whether the lack of Th1 type response in these tumors is accompanied by elevation in Th17 type of response or not. Considering the critical role of inflammation in cancer development and progression and based on the reciprocal interaction between IL-17A and IL-6, we hypothesize that there is a difference between IL-17A and IL-6 production in benign and malignant forms of CNS tumors. Moreover, it is logical to assume that the levels of these two cytokines in sera of patients with CNS tumors differ from that of healthy individuals.

Materials and Methods

Subjects

This study was approved by the ethics committee of Shiraz University of Medical Science (SUMS). The participants were informed about the aim of this study as well as safety and security measures before their consents were obtained. The study groups consisted of 38 glioma, 24 meningioma and 18 schwannoma patients as well as 26 healthy controls. The patients were referred to our laboratory by our collaborating Neurologist (March 2007-March 2012) and the diagnosis was completed based on pathology reports. All the samples were taken before surgery and/or before therapy. The pathological and demographical data of patients as well as grading (based on WHO grading system 2007) were extracted from patients' hospital files at the time of sampling (Louis et al., 2007). The demographic data obtained by a questionnaire and pathological characteristics of patients and controls are shown in Table 1.

Sampling

Two ml Blood was taken from patients and controls by venipuncture method after informed consent. The sera were collected by centrifugation and were kept in -20°C until used. The levels of IL-17A and IL-6 in sera were measured by commercial ELISA assays (Sandwich biotin-avidin method, eBioscience, USA).

IL-17A and IL-6 ELISA. The ELISA assay was performed by biotin-avidin commercial ELISA assays according to manufacturer's instructions (BMS2017 and

Table 1. Characteristics of the Patients and Controls

Characteristics		Glioma pts	Meningioma pts	Schwannoma pts	Healthy controls
Gender	Male (no.)	19	6	6	10
	Female (no.)	19	18	12	16
Grade	High (no.)	20	NK*	NK*	-
	Low (no.)	18	NK	NK	-
Age	Mean \pm SD	34.7 \pm 19.2	54.5 \pm 14.2	41.2 \pm 16.1	48.6 \pm 18.4
	(range, yrs)	(3-75)	(30-83)	(19-80)	(19-77)
Concentration of (pg/ml)					
	IL-17A	0.29 \pm 0.54	0.03 \pm 0.15 ^y	0.16 \pm 0.68 ^y	0
	IL-6	2.34 \pm 4.35	3.81 \pm 10.14	3.85 \pm 4.86	4.67 \pm 4.32

*NK=Not Known, ^yOnly one case positive

BMS213/2, ebioscience, USA). Briefly, sera were diluted 1:2 and added to the plates. The standard sera containing known concentrations of IL-17A (or IL-6) were added to control wells. Then 50 μ l of BIOTIN-labeled Anti-Human IL-17A (or Anti-Human IL-6) antibody was added to the wells and the plate was incubated for 2 hrs in the room temperature with frequent shaking in 100 rpm. The wells were then washed by washing buffer for 4 times and then 100 μ l of Streptavidin enzyme conjugate was added to each well. After 1 hr of incubation, the plate was washed and 100 μ l of the substrate TMB was added. After 10 minutes of incubation in the dark, the stop solution was added and the optical densities (OD) were measured by an ELISA reader (Anthos, Austria). The ODs were then transformed to concentration by using the standard curve obtained in each test.

Statistical analysis

Using SPSS software (version 11.5, SPSS Inc., Chicago, IL., USA), Student's t-test and Mann-Whitney signed rank test were used to compare the mean level of IL-17A between groups. Chi-Square and Kruskal-Wallis tests were used to compare IL-17A between multiple groups.

Results

IL-17A and IL-6 levels in patients and controls

The level of IL-17A was elevated in all CNS tumors compared to healthy controls (Figure 1A, one tailed $p=0.035$, student t-test). Eleven out of 80 patients (glioma+meningioma+schwannoma) were found positive for IL-17A in the detection limit of our test while none of the control subjects were positive (one tailed $p=0.038$, Chi-square Exact test).

In contrast, the mean levels of IL-6 in sera of all 80 patients was not significantly different from the controls (Figure 1B, one tailed $p=0.397$, student t-test). Sixty-six out of 80 patients (glioma+meningioma+schwannoma) and 24 out of 26 controls were positive for IL-6 in the

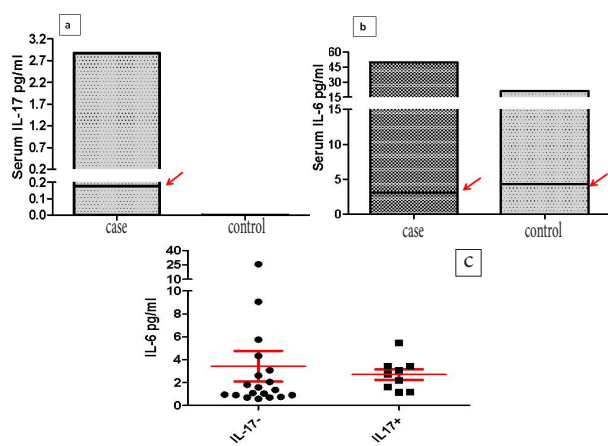


Figure 1. Cumulative Levels of IL-17A and IL-6 in Both Types of CNS Tumors. A) Comparisons of IL-17A, $p=0.035$ and B) IL-6 serum levels, $p=0.397$ between patients with brain tumor and controls. student t-test was used for comparing the means between groups. Red arrow shows the mean value, student t-test; C) The $p=0.067$, Mann Whitney rank test

serum and the difference in the frequency of positive cases did not reach the significant level (one tailed $p=0.187$, Chi-square Exact test).

The mean IL-17A and IL-6 levels in patients and controls are represented in Table 1.

IL-17A levels in patients and controls

The comparison of IL-17A in glioma, meningioma and schwannoma patients with controls revealed a significantly higher level of IL-17A in glioma patients compared to the schwannoma ($p=0.01$), meningioma ($p=0.01$) and healthy (0.0014, Kruskal-Wallis test) individuals. Only one of the meningioma patients and one of the schwannoma patients showed an elevation in IL-17A (Figure 2).

IL-6 levels in patients and controls

In contrast to our expectation, the lowest level of IL-6 was detected in sera of glioma patients (Figure 3, $p=0.026$, Kruskal-Wallis test). The IL-6 level did not differ significantly between benign CNS tumors and control subjects (Figure 3). However, when the patients were categorized based on IL-17A to positive and negative cases, those with IL-17A in their sera showed lower levels of IL-6 but this difference did not reach the significant level (Figure 1C).

Increased levels of IL-17A and decreased levels of IL-6 in glioma patients with age

The comparison of the cytokine levels in glioma patients in different age groups (i.e. ≤ 30 or >30 years of age) showed that there was no patient less than 30 with IL-17A elevation and the elevation was restricted to patients who were older than 30 years of age (Figure 4A,

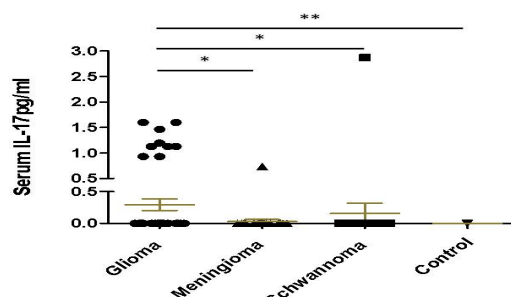


Figure 2. Higher Level of IL-17A in Glioma Patients. Mean Serum IL-17A Levels were Compared Between Patients with Glioma, Meningioma or Schwannoma with Healthy Subjects by Kruskal-Wallis Test

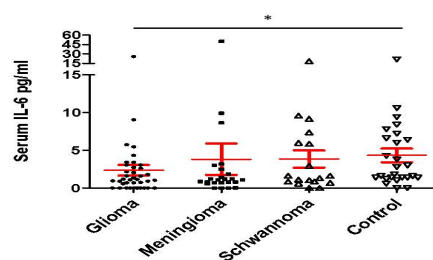


Figure 3. Lower Level of IL-6 in Glioma Patients. Mean serum IL-6 levels were compared between patients with glioma, meningioma or schwannoma with healthy subjects by Kruskal-Wallis test, $*p=0.026$, Kruskal-Wallis

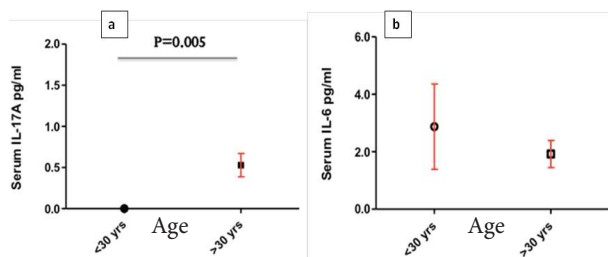


Figure 4. IL-17A and IL-6 Level in Glioma Patients Based on Age. A) Comparisons of IL-17A and B) IL-6, serum levels between glioma patients older than 30 years and younger than 30 years of age. Mann-Whitney signed rank test was used for comparing the means between groups

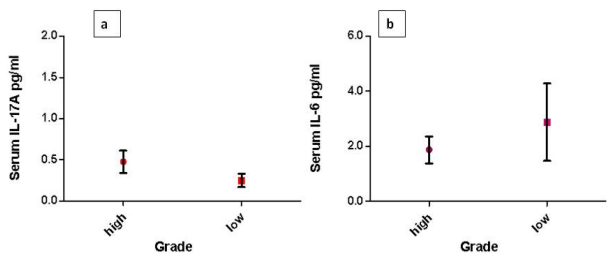


Figure 5. IL-17A and IL-6 Levels in Glioma Patients Based on Grade of Tumor. A) Comparisons of IL-17A and B) IL-6 (B) serum levels between low grades and high grades of glioma. mann-whitney signed rank test was used for comparing the means between groups

Table 2. Cytokine Levels in Different Grades of Glioma Based on W.H.O. Grading

	IL-6 (pg/ml)	IL-17A (pg/ml)
Grade I (n=10)	4.02±7.80	0.19±0.39
II (n=10)	2.16±2.97	0.11±0.36
III (n=12)	1.41±1.45	0.35±0.64
IV (n=6)	1.74±1.55	0.65±0.73

Table 3. Cytokine Levels in Different Genders Among Glioma Patients

	IL-6 (pg/ml)	IL-17A (pg/ml)
Female (n=19)	2.98±5.90	0.32±0.55
Male (n=19)	1.71±1.83	0.27±0.55

$p=0.005$). On the contrary, the level of IL-6 decreased with age and it was higher in glioma patients who were ≤ 30 years of age. Although this difference did not reach the significance level (Figure 4B, $p=0.635$).

Different patterns of IL-17A and IL-6 elevation based on the grade of glioma tumors

Low grade gliomas showed lower levels of IL-17A and higher levels of IL-6 in serum, while high grade gliomas showed higher IL-17A and lower IL-6 levels (Figure 5A and 5B). These differences, however, did not reach the significant level.

No difference in the level of IL-6 and IL-17A was found between the glioma, meningioma and schwannoma patients based on gender. Tables 2 and 3 show the level of IL-6 and IL-17A in different grades and different genders in glioma patients, respectively.

Discussion

The first finding of our study was an increased level of IL-17A in sera of patients with CNS tumors. While none of the healthy controls and only one meningioma and one schwannoma patient had IL-17A in their sera, elevation of this cytokine was confined to glioma patients. Previous studies have indicated an increase in the expression of IL-17A, as well as recruitment of Th17 cells to the site of gastric tumors (Zhang et al., 2008). In a recent study, we observed elevated levels of IL-17A in bladder cancer patients in southern Iranian patients (Doroudchi et al., 2013). Tumorigenic effect of IL-17A in bladder and melanoma cell lines has been shown to be related to the signal transducer and activator of transcription (Stat-3) pathway signaling (Wang et al., 2009). IL-17A induces IL-6 production, which in turn upregulates pro-survival and pro-angiogenic genes. Thus the tumor promoting Th17 response can in part be linked to IL-6-Stat-3 pathway. In this model, injection of tumor cell lines to IL-17A KO mice resulted in a decrease in the tumor volume, while lack of IFN- γ gene resulted in the production of large tumors. Moreover, increase in the tumor volume was reported to be associated with the increased expression of Stat-3, anti-apoptotic and angiogenic factors. Whether IL-17A has the same effect in gliomas remains to be investigated. However, it is shown that Stat-3 is highly activated in glioblastoma multiforme (GBM) cells (Rahaman et al., 2002). The self-renewal capacity of GBM stem cells is also suggested to be regulated by Stat-3 pathway (Sherry et al., 2009).

Much to our surprise the level of IL-6 in sera of glioma patients was significantly lower than that of meningioma patients and healthy controls. Previous studies have shown that IL-6 level positively correlates with the activity and exercise levels (Reihman et al., 2013; Sim et al., 2013). Considering the effect of even low-level exercise on the IL-6 levels in plasma, the highest levels of IL-6 that was observed in healthy controls may be explicable by a more active lifestyle. The expression of IL-1 β , TNF- α and IL-6 genes in brain neoplasms and meningiomas has been reported (Merlo et al., 1993). However, in the few case-reports on the serum level of IL-6 in meningioma patients, normal or increased levels of IL-6 in serum is reported (Rittierodt et al. 2001; Arima et al., 2005; Sato et al., 2010). The local increased level of IL-6 is also shown to contribute to the development of brain edema in meningiomas (Park et al., 2010). The increased level of IL-6 in gliomas, however, has been restricted to GBM cases (Meir et al., 1990; Tofaris et al., 2002; Van Lee et al., 2009).

In our study, the patients older than 30 years of age had lower levels of IL-6 compared to patients younger than 30 years of age, whilst IL-17A was only detected in sera of patients older than 30 years. A negative correlation between IL-17A levels and aging in healthy individuals is already reported while the level of IL-6 and other inflammatory cytokines increases with age (Alvarez-Rodríguez et al., 2012). On the other hand, the tumor cells can produce different cytokines and growth factors disrupting the natural pattern of cytokine production.

Therefore, the higher IL-17A in glioma patients is not attributed to aging process but more likely related to the tumors intrinsic properties.

Another finding of our study was the higher levels of IL-17A in higher grades of glioma compared to the lower grades of the disease. This was contrary to the decreased levels of IL-6 in higher grades of glioma. Although this difference did not reach the significant level, this observation is noteworthy in respect to the notion that IL-6 independent Stat-3 signaling pathways induced by genetic and epigenetic changes in epithelial tumors can circumvent the need for extrinsic IL-6 triggering of its receptor (Jarnicki et al., 2010). Stat-3 in a constitutively activated state has been observed in many human cancers, including breast, head and neck, prostate, melanoma, and thyroid cancer. Stat-3 is also activated in a high percentage of GBMs and mouse Neuron SCs, probably playing a role in maintaining self-renewal (Sherry et al., 2009). Interestingly, the kinetic and levels of Stat-3 phosphorylation in tumor cells bearing mutations in SOCS-3 inhibitor of IL-6 signaling is different from that of normal cells (Jarnicki et al., 2010). The deregulated Stat-3 signaling results in constitutive high level expression of anti-apoptotic and proliferative factors in epithelial cancer cells (Sherry et al., 2009). Knowing the fact that the majority of low grade astrocytomas tend to transform to high grade tumors with more aggressive behavior, it remains to be clarified whether the high grade glioma tumors gain ligand (IL-6) independent IL-17A mediated growth and proliferation during their progression. At the same time, the small sample size of the studied patients (although inevitable) is one of the limitations of our study and can be overcome in future studies by the already established database of CNS tumors in our institute and continuous additions to the samples over the years.

In conclusion, we report elevated serum levels of IL-17A in high grade gliomas among elder patients. A concomitant decrease in the IL-6 serum level in the same group of patients suggests a stage-specific modulation of inflammatory cytokines during glioma progression. Investigating the possible mutations in the Stat-3 signaling molecules or inhibitors will provide further information on the biology of the tumor progression and evasion mechanisms from the immune system. Elevation of IL-17A in the sera of patients bearing glioma but not meningioma and schwannoma tumors presents this cytokine as a potential biomarker of glioma. Moreover, there may be the possibility of immunotherapeutic use of anti-IL-17A antibodies in glioma patients.

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