

RESEARCH ARTICLE

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Serum Levels of APRIL Increase in Patients with Glioma, Meningioma and Schwannoma

Hamed Fouladseresht¹, Seyyed Mohyeddin Ziaee¹, Nasrollah Erfani^{1,2}, Mehrnoosh Doroudchi^{1,2*}

Abstract

Objective: Brain tumors are of high mortality and morbidity for which there is still no cure. The TNF family cytokine, A Proliferation Inducing Ligand (APRIL), is shown to help proliferation and development of tumor cells. We assessed serum levels of APRIL in patients with glioma, meningioma and schwannoma in comparison to healthy individuals. **Methods:** Peripheral blood samples of 68 patients with brain tumors, divided into three groups of gliomas (n=25), meningiomas (n=30) and schwannomas (n=13), as well as 45 healthy individuals were obtained. Serum samples were prepared and stored in -40°C until usage. Using a commercial ELISA method, APRIL concentration was measured in each serum sample. The obtained data were then analyzed using SPSS software. **Results:** APRIL serum levels were higher in all patients compared to the controls (P<0.001). Moreover, APRIL serum levels were higher in each of the tumor bearing groups (gliomas, meningiomas and schwannomas) in comparison to the controls (P<0.001, <0.001 and =0.001, respectively). Comparing APRIL between the patients groups showed no significant difference. Age and gender showed no significant correlation with serum APRIL levels, although the age of patients in glioma group was significantly lower than controls (P=0.017). The serum APRIL levels in gliomas with histological grade showed no difference, but in meningiomas, it was lower in tumors with higher grades (P= 0.011). **Conclusion:** Increased serum levels of APRIL in patients with meningioma and schwannoma as well as glioma may indicate a common role of this cytokine in brain tumors.

Keywords: APRIL- glioma- meningioma- schwannoma

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Introduction

Brain tumors are responsible for 20% of childhood malignant tumors (Kaye, 2009). Primary brain tumors are among the most important health problems worldwide. They are responsible for 2% of total cancer deaths and include the most common type of severe tumors in young people. Primary brain tumors are classified based on cellular source where neuroepithelial tumors include gliomas, pineal tumors, neuronal tumors and medulloblastoma, nerve sheath tumors include vestibular schwannoma or acoustic neuroma, and other types include meningeal tumor (Meningioma), germ cell tumor, lymphomas, metastatic tumors and tumor-like abnormalities (Martin-Villalba et al., 2008; Louis et al., 2016). The most common of those are gliomas (52%), meningiomas (15%) and schwannomas (8%) (Whittle et al., 2004; Lu-Emerson and Norden, 2010). Gliomas and meningiomas comprise more than 66.2% of the primary brain tumors (Porter et al., 2010). Gliomas are a collection of heterogeneous tumors, including astrocytomas which named based on their resemblance

to astrocytes (Martin-Villalba et al., 2008; Louis et al., 2016). 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 (Whittle et al., 2004; Wiemels et al., 2010). Schwannomas are benign tumors originating from the schwann cell sheath surrounding the nerves (Fong et al., 2011; Zhang et al., 2012). Despite their high mortality and morbidity, many of the diagnostic and treatment protocols for treating brain tumors are not effective. These treatments are both invasive (surgical removal) and ineffective so that the average life expectancy for patients undergoing different treatments (chemotherapy and radiotherapy) is only in the order of months (Reardon et al., 2006; Polyzoidis and Ashkan, 2014). In addition, surgery cannot be performed on most of the meningiomas due to the location of the tumor. In this case, the patient is usually being followed up for the tumor progression and radiotherapy is also performed (Minniti et al., 2009; Jiang and Uhrbom, 2012). Therefore,

¹Department of Immunology, ²Institute for Cancer Research, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran. *For Correspondence: mdoroud@sums.ac.ir

the demand for more effective diagnosis and treatments is real. Nowadays, advances in the immunodiagnostic and immunotherapeutic approaches are promising (Polyzoidis and Ashkan, 2014), therefore identifying and introducing appropriate immunological targets for diagnostic and therapeutic use is imminent among which, cytokines can be one group of candidates. Increasing the expression of IL-10 in gliomas, which results in suppression of the immune system and progression of the disease, is already shown (Beckebaum et al., 2004; Alcocer-González et al., 2006). Also, in astrocytomas and gliomas, the increased serum levels of TGF- β 2 and IL-6 have been associated with the progression of those diseases (Kjellman et al., 2000; Tchirkov et al., 2007; Saidi et al., 2009). In addition, the associations of IL-8, TGF- β 1 and VEGF with different brain tumors are reported (Brat et al., 2005; Christofides et al., 2015; Taurone et al., 2015). The role of TNF family of cytokines in the development and progression of brain tumors is variable. For example, the TRAIL molecule has anti-tumor properties in gliomas (Christofides et al., 2015), while TNF- α , from the same family, induces the differentiation, growth, migration and activation of glial cells and ultimately induces tumor progression (Taurone et al., 2015). A proliferation-inducing ligand (APRIL) is also a member of the TNF superfamily, also known as tumor necrosis factor ligand superfamily member 13A (TNFSF13A), TALL2 and CD256 (Hahne et al., 1998). It can act in a membrane-bound form (mAPRIL) or as a soluble cytokine (sAPRIL) in an endocrine, paracrine or autocrine manner. APRIL is recognized by the cell surface receptors: a) trans membrane activator, calcium modulator and cyclophilin ligand (CAML) interactor (TACI), and b) B cell maturation antigen (BCMA) (Schneider et al., 2002). In addition, heparan sulfate proteoglycans (HSPG) can bind to APRIL, and act as a scaffold for proper signaling of the molecule (Hendriks et al., 2005; Ingold et al., 2005). The gene encoding APRIL is located on human chromosome 17p13, which promotes cell survival and proliferation. In normal conditions, APRIL is expressed at low levels by various normal cells, such as monocytes, macrophages, dendritic cells, osteoclasts, adipocytes, keratinocytes, liver cells, B cells and T cells. In vitro studies suggest that, APRIL can cause B cell and T cell proliferation and survival (Bossen et al., 2008; Kimberley et al., 2009). *In vivo*, it affects thymus-independent (TI) B-cell responses when produced by dendritic cells and can directly signal class switching (Litinskiy et al., 2002). Moreover, IgA class switching *in-vivo* appears to depend critically on APRIL (Castigli et al., 2004). In pathologic conditions, such as tumor and autoimmune diseases, APRIL is produced very rapidly. The expression of APRIL in hematopoietic malignancies such as ALL, CLL, FCL, NHL and MM has been known for quite some time, however, it is interesting that APRIL is abundantly expressed in many solid tumor tissues as well (Novak et al., 2002; Novak et al., 2004; Lemancewicz et al., 2013; Sun et al., 2014; Li et al., 2015). Immunohistochemical and serum studies have indicated that the levels of APRIL in tumors and sera are higher in patients with solid tumors than in healthy individuals. This finding suggest that APRIL may function as an autocrine or endocrine growth

factor during tumorigenesis (Roosnek et al., 2009). The existence of tumor specific receptor for APRIL, which was shown on HT29 colon carcinoma, A549 lung epithelial cells and NIH-3T3 fibroblasts cells is of utmost importance (Hahne et al., 1998; Rennert et al., 2000). APRIL increases the proliferation of tumor cells through binding to HSPG and activates different signaling pathways, such as caspases, NF- κ B or MAP kinase including c-Jun NH2-terminal kinase (JNK) or extracellular signal-regulatory kinase (ERK) (Hendriks et al., 2005; García-Castro et al., 2015). The expression of APRIL at the level of mRNA and protein in tumor tissue is already shown (Hžeka and Hžekci, 2006; Mhaweche-Fauceglia et al., 2006; Mhaweche-Fauceglia et al., 2008). Moreover, one study investigated the serum levels of APRIL in patients with glioblastoma in comparison to healthy controls (Hžeka and Hžekci, 2006).

In the current study, we asked if the serum level of APRIL is different in brain tumors with different degrees of aggression. Therefore, we measured the levels of APRIL in the sera of patients with glioma, schwannoma and meningioma in comparison to healthy controls.

Materials and Methods

Subjects

In total, 68 patients with brain cancer were selected from among patients who referred to the hospitals affiliated to the Shiraz University of Medical Sciences (SUMS, Shiraz, Iran). The distribution of patients according to brain tumor type was described as follows: 25 patients having gliomas, 30 patients having meningioma, and 13 patients having schwannoma. The demographic data obtained by a questionnaire and pathological characteristics of patients are shown in Table 1. None of the patients had received immunotherapy, radiotherapy or chemotherapy before sampling. Brain cancer staging was done by collaborating oncologists based on the surgical and pathological reports. Control group included 45 healthy individuals who were selected from among healthy blood donors of the same age range and gender referred to Fars Blood Transfusion Center. They were examined by a physician and were evaluated for underlying diseases, including: allergy, asthma, cancer, immunodeficiency, autoimmune diseases and others immunological disorders. Then, they were asked for recent cigarette smoking, use of any drugs, surgery, trauma, vaccination and infectious diseases. All items listed above were also considered as exclusion criteria. This study was evaluated and approved by the Ethics Committee of Shiraz University of Medical Science (EC-SUMS). Informed consent was given by all participants for blood donation and data publication.

Sampling

Peripheral blood samples (3 ml) were obtained from all participants and the sera were separated and stored at -70°C until use.

Measurement of APRIL in the serum

The serum levels of APRIL were measured by commercial pre coated sandwich ELISA plates according

to manufacturer's instructions (R and D Systems, Minneapolis, USA). The serum levels of APRIL were quantitated by using standard samples with known concentrations of cytokine, provided by the manufacturer and expressed as ng/mL. Briefly, after adding 100 μ L of assay diluent RD1-68 to each well, the sera were added to the plates. The standard sera containing known concentrations of APRIL were added to control wells. Then, the wells were washed by washing buffer for 4 times. 200 μ L of biotin-labeled anti-human APRIL 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 washed by washing buffer for 4 times and 200 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 TMB substrate 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 transformed to concentration by using the standard curve obtained in each test.

Statistical analysis

After sample collection, data were analyzed using the SPSS software (version 11.5, Chicago, IL, USA). Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the normal distribution of data. The student's t-test and Mann-Whitney test were used for comparison of APRIL concentration between groups. Also, Chi-Square test was used to compare grade and gender between multiple groups. P values less than 0.05 were considered significant.

Results

Elevated serum levels of APRIL in the patients with brain tumor

The mean serum levels of APRIL in patients with brain cancer and healthy individuals are demonstrated in Table 2. The mean serum level of APRIL in patients with brain cancer (gliomas, meningioma and schwannoma) was significantly higher than that of healthy controls (Figure 1, $P < 0.001$). Also, there was a significant difference in the levels of APRIL between patients with glioma, schwannoma and meningioma with healthy individuals (Figure 2, $P < 0.001$). No significant difference regarding

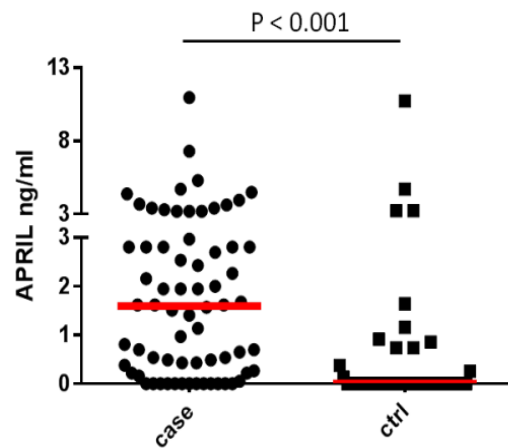


Figure 1. The Distribution of APRIL Serum Concentration in the Patients with Brain Tumors (Total) Compared to Controls

the mean serum levels of APRIL was observed between different brain tumor types ($P > 0.05$).

Serum levels of APRIL increased with advancing of tumor grade

There was a significant difference between grades

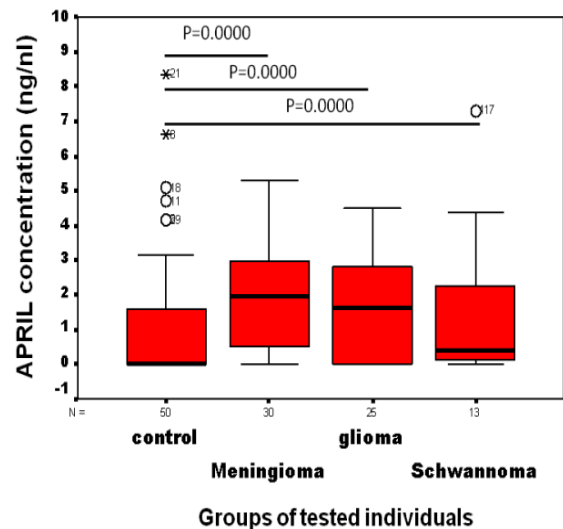


Figure 2. Comparison of APRIL Levels between Patients Groups (Glioma, Meningioma, Schwannoma) and Controls.

Table 1. Characteristics of the Patients and Controls

Characteristics	Glioma	Meningioma	Schwannoma	Healthy controls
Gender				
Female (no.)	12	10	4	26
Male (no.)	13	20	9	17
Age (yrs.)	41.5 \pm 14.7	47.9 \pm 19.1	45 \pm 18.4	52.7 \pm 14.4
Grade				
I (no.)	ND	8	ND	
II (no.)	4	ND	ND	
III (no.)	4	7	ND	
IV (no.)	5	ND	ND	

ND, Not Determined

Table 2. The Serum Levels of APRIL in the Patients with Different Brain Tumors in Comparison with Healthy Individuals.

Groups	Sub groups	APRIL (ng/ml)	Total (ng/ml)
Patients	Gliomas	1.89 ± 2.3	1.84 ± 1.95
	Meningioma	1.92 ± 1.52	
	Schwannoma	1.57 ± 2.23	
Healthy			0.64 ± 1.83

Table 3. The Serum Levels of APRIL in Brain Tumors with Different Grades

Characteristics	Glioma (ng/ml)	Meningioma (ng/ml)	Schwannoma (ng/ml)
Grade			
I (no.)	ND	2.36 ± 1.03	ND
II (no.)	1.81 ± 1.33	ND	ND
III (no.)	0.97 ± 1.51	0.79 ± 1.09	ND
IV (no.)	3.32 ± 4.41	ND	ND

ND, Not Determined

of meningioma regarding the mean serum levels of APRIL ($P < 0.001$). Table 3 shows the serum level of APRIL in patients with different grades of glioma and meningioma. Results showed a significant relationship between meningioma grade and serum level of APRIL ($P = 0.011$). However, there was no significant difference in the serum level of APRIL between the grades of the glioma ($P = 0.627$). In each of the patient groups, the level of APRIL was higher in females than males. However, no difference in the level of APRIL was found between glioma, meningioma and schwannoma based on gender. Table 4 shows the level of APRIL in gliomas patients with different genders.

Discussion

In this study, we demonstrated that APRIL levels increase in the sera of patients with in different types of brain tumor, suggesting that up-regulation of APRIL is involved in their pathogenesis. Despite being rare, brain tumors are deadly and debilitating. Tumor cells are self-renewable, insensitive to anti-growth signals, have stable angiogenesis, tissue attack and metastasis, high proliferation potential and can escape from apoptosis and immune system (O'Brien et al., 2010; Ziyad and Iruela-Arispe, 2011). Gene expression disorders and cytokine production are among the most important phenomena in the pathogenesis of brain tumors among which APRIL is a noble molecule. APRIL is a cytokine that induces the survival and proliferation of tumor cells (Planelles et al., 2004; Mhawech-Fauceglia et al., 2006; Schwaller et al., 2007). Our finding is in accordance with previous studies, although their focus has been mostly on the expression of APRIL in the tumoral tissue (Mhawech-Fauceglia et al., 2006; Moreaux et al., 2009; Xian et al., 2014; García-Castro et al., 2015; Lascano et al., 2015). Moreover, the studies in gliomas are more frequent and comparison between these three brain tumor

Table 4. The Level of APRIL (ng/ml) in the Sera of Patients Based on Gender

Groups	Female	Male	P value
Glioma	2.16 ± 3.03	1.64 ± 1.41	0.956
Meningioma	1.95 ± 1.63	1.85 ± 1.36	0.86
Schwannoma	1.83 ± 2.5	0.99 ± 1.6	0.487

types is scarce (Freije et al., 2004; Moreaux et al., 2009; Pelekanou et al., 2013). Our finding on the APRIL level in glioma is in accordance with a previous study that showed patients with multiple-gliomoblastoma tumors had a higher APRIL serum level than controls (Iłzecka and Iłzecki, 2006). We, too, found that APRIL increases in the serum in advanced stages of gliomas. These data represent that the elevation of the APRIL levels may contribute in the gliomas progression and development.

The exact mechanisms which are responsible for the elevation of the APRIL levels in patients with gliomas remain to be clarified. But in vitro studies on breast tumor cell lines have shown that TLR3 and NF-κB are associated with tumor cell survival resistance and are crucial for promoting of the APRIL gene expression (Cao and Karin, 2003; Xu et al., 2012; Yu et al., 2012; García-Castro et al., 2015). There is evidence that damage-associated molecular pattern (DAMP) or endogenous molecules released from damaged tissues cause TLRs activation and tumor progression (Yu et al., 2012; García-Castro et al., 2015). This process is one of the probable links between TLRs and expression of APRIL and its receptor (HSGPs). Co-expression of APRIL and HSGPs enables autocrine proliferation of tumor cells. APRIL also binds HSPG on the tumor cell surface, which is critical for the proliferation-mediated effect (Hendriks et al., 2005). APRIL causes phosphorylation of JNK1/2, ERK1/2 and p38 and the overexpression of these MAP kinases are shown in tumor cells associated with cell proliferation and survival (Adeyinka et al., 2002). In addition to its autocrine role as a tumor-promoting factor, APRIL paracrine signaling is described in cancers such as leukemia or glioblastoma (Planelles et al., 2008). Interestingly, APRIL expression not only increases in tumor cells but also in tumor-infiltrating leukocytes, and in “normal” epithelial cells near the tumor area providing a possible source of APRIL in serum (Pelekanou et al., 2008). In contrast to gliomas the serum levels of APRIL decreased with grade of meningioma. However, the lack of grading information on half of the meningioma cases hampers any conclusion at this point. A possible gender difference in the APRIL serum levels needs to be investigated in studies with larger sample sizes. Moreover, it would be interesting to see if the source of APRIL production in different brain tumors is different.

In conclusion, elevated serum levels of APRIL in brain tumors suggest that APRIL may be an important cytokine for progression of these tumors. This preliminary report provides a basis for the study of the TNF family members in a large cohort of patients to investigate its possible prognostic and therapeutic values.

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Compliance with ethical standards

This study was evaluated and approved by the Ethics Committee of Shiraz University of Medical Science (EC-SUMS). Informed consent was given by all participants for blood donation and data publication.

Statement conflict of Interest

The authors declare no conflict of interest.

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