

Plasma Levels of Glucose and Insulin in Patients with Brain Tumors

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ABSTRACT : In the last years there were many authors that suggest the existence of an association between different components of metabolic syndrome and various cancers. Two important components of metabolic syndrome are hyperglycemia and hyperinsulinemia. Both of them had already been linked with the increased risk of pancreatic, breast, endometrial or prostate cancer. However the correlation of the level of the glucose and insulin with various types and grades of brain tumors remains unclear. In this article we have analysed the values of plasma glucose and insulin in 267 patients, consecutively diagnosed with various types of brain tumors. Our results showed no correlation between the glycemia and brain tumor types or grades. High plasma levels of insulin were found in brain metastasis and astrocytomas while the other types of brain tumors (meningiomas and glioblastomas) had lower levels of the peptide. The levels of insulin were also higher in brain metastasis and grade 3 brain tumors when compared with grade 1, grade 2 and grade 4 brain tumors.

KEYWORDS: brain tumors, relations, glucose, insulin

Introduction

Along with its concomitant diseases (obesity, dislipidemia, hyperglycemia, hypertension), the metabolic syndrome may be an important etiologic factor for the development and progression of several neoplasms.[1]

Several studies support the idea that metabolic syndrome may be involved in the etiology, progression or outcome of some cancers like: prostate, colorectal, liver, biliary tract, gallbladder, breast, and endometrial.[1-8]

Until now, the data to demonstrate the relationship between metabolic syndrome or it's components and various types of brain tumors is very small. In 2012 Edlinger et al published the Me-Can cohort study which assessed the relationship between metabolic syndrome and the risk of brain tumors. The study revealed that increased blood pressure was associated with an increased risk of brain tumors especially meningioma, while diastolic blood pressure (DBP) and triglycerides were related to an elevated risk of high-grade glioma. However the study had its limitations, one of them being that only meningiomas and high-grade gliomas were taken into account. [9]

Two important components of metabolic syndrome are hyperglycemia and

hyperinsulinemia. Hyperglycemia represents the elevation of blood glucose concentrations above the normal range. Hyperglycemia was associated with increased risk of pancreas neoplasm, malignant melanoma, endometrial and breast cancer. [10, 11] Some authors already studied diabetes or the increased levels of glucose as risk factors for brain tumors. Unfortunately, the results of these rather large studies are inconclusive.[12-15] The interrelation between glucose and insulin levels in metabolic syndrome is well known: high glucose concentration is caused by a decrease in the production of insulin, a decrease in the action of insulin, or a combination of the two abnormalities. Hyperinsulinemia is associated with hypertension, obesity, dyslipidemia and glucose intolerance which are all parts of metabolic syndrome.. Hyperinsulinemia has also been shown to be linked with breast, endometrial and prostate cancer.[16-18]

To our best knowledge hyperglycemia and hyperinsulinemia have not been studied on all types of brain tumors. The objective of our study was to evaluate the possible correlation between glucose levels, insulin levels and various types of brain tumors.

Material and Methods

1. Patients

In this study were included two hundred and sixty-seven patients consecutively diagnosed with brain tumors in the 3rd Neurosurgery Clinic of Bagdasar-Arseni Hospital, Bucharest, Romania. The time frame for the recruitment of the patients was 2006 -2012. Brain tumors were defined as tumors of the brain indicated by clinical features and CT / MRI examination and verified histopathologically after surgery. The histopathology grading was performed in accordance with the most recent World Health Organization (WHO) classification (the fourth revision, 2007).[19] The median age of the 267 patients was 56 years (range 15-83 years).

All patients were free of corticotherapy or antineoplastic drugs at study enrollment. Six patients were included in the first 24 hours from symptoms onset, before receiving any specific medication. The rest of 261 patients were free of corticotherapy for at least two weeks prior to study enrollment.

Our group included 18 patients previously diagnosed with type II Diabetes Mellitus and receiving antidiabetic drugs.

2. Methods

Blood samples were drawn from overnight-fasting brain tumor patients. Plasma to determine glycemia and insulin was separated within one hour of sampling and stored at -70°C until assayed.

3. Determination of glycemia

We determined plasma glycemia by using Reagent kit for quantitative determination of glucose concentration which is an Enzymatic Colorimetric Method. The kit was provided by Diagnosticum Inc. 1ml of working reagent was pipetted into separate cuvettes of 1cm light path. One cuvette was for the blank and we added 10µl of distilled water. The second cuvette was for the standard and we added 10µl of standard from the kit. The other cuvettes were for the samples and we added 10µl of each sample in each cuvette. We determined the absorbance spectrophotometrically at 505nm.

The calculations were made using the following algorithm:

$A_{\text{sample}} / A_{\text{standard}} \times C_{\text{standard}} = C_{\text{sample}}$;
where A = absorbance and C = concentration.

The reference values for serum glucose are : 3.89 – 5.84 mmol/l (70-105mg/dl).

4. Determination of plasma insulin

We determined the plasma insulin by using the Invitrogen Human Insulin Kit which is an Enzyme Linked-Immuno-Sorbent Assay (ELISA). 50µl of each standard, control or sample were pipetted into the 96 wells of the insulin antibody-coated microtiter plate. Then, we added a detector monoclonal antibody labeled with horseradish peroxidase (HRP). After an 30 minutes of room temperature incubation, the wells are discarded by their content and washed 3 times with washing solution. Following the washing step a substrate solution containing tetramethylbenzidine (TMB)-H₂O₂ is added into each well. After 15 minutes of incubation at room temperature and in the dark the reaction is stopped with HCl and the microtiter plate is read spectrophotometrically within 1 hour at 450nm. The intensity of color is directly proportional to the concentration of insulin in the original specimen.

5. Statistical analysis

Statistical analysis was performed by the Biostatistics Department of the University of Medicine and Pharmacy of Craiova, Romania, using Microsoft Excel (Microsoft Corp., Redmond, WA, USA), together with the XLSTAT add-on for MS Excel (Addinssoft SARL, Paris, France). To test the normality of the data we used the Anderson-Darling and Shapiro-Wilk tests.

Because the study involved a numerical comparison between more than 2 groups of patients that did not have a normal (gaussian) distribution, the nonparametric Kruskal-Wallis test was primarily used, although we also used the ANOVA test, mainly for the post-hoc comparison (Tuckey HSD and Fisher LSD test) to detect significant differences between pairs of groups.

Results

1. Brain tumors histological types

Table 1 shows the distribution of various types of brain tumors in our study group. Of the 267 patients studied, 32.96% were diagnosed with meningiomas, 29.21% with glioblastomas, 10.49% with cerebral metastasis and 8.24% were diagnosed with astrocytomas. The other 19.85% had other types of brain tumors like: schwannoma, meduloblastoma, meningeal sarcoma, ependimoma, oligodendroglioma, hemangiopericitoma , and so on.(Fig.1; Table1)

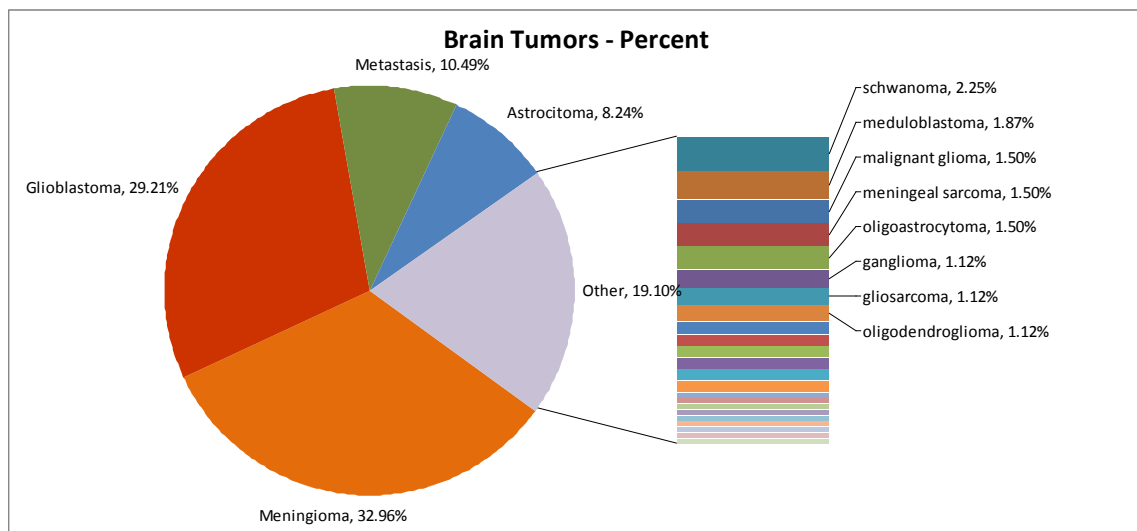


Fig.1. Types of studied brain tumors

Table 1. Types of brain tumors studied

Diagnosis	Total	Percent
Meningioma	88	32.96%
Glioblastoma	78	29.21%
Metastasis	28	10,49%
Astrocitoma	22	8.24%
Schwannoma	6	2.25%
Meduloblastoma	5	1.87%
malignant glioma	4	1.50%
meningeal sarcoma	4	1.50%
Oligoastrocytoma	4	1.50%
Ganglioma	3	1.12%
Gliosarcoma	3	1.12%
Oligodendroglioma	3	1.12%
Ependimoma	2	0.75%
Hemangiopericitoma	2	0.75%
Limfoma	2	0.75%
Neurocitoma	2	0.75%
pituitary adenoma	2	0.75%
PNET	2	0.75%
Chordoma	1	0.37%
Condrosarcoma	1	0.37%
Disembryoplastic neuroepithelial tumor	1	0.37%
Ganglioneuroblastoma	1	0.37%
Hemangioblastoma	1	0.37%
liposarcoma mixoid	1	0.37%
Miopericitoma	1	0.37%
Others	53	19.10%
Total	267	100.00%

According to WHO system, four malignancy grades are recognized. In Fig.2 and Table 2 we can see that 32.58% of the patients taken in this study were diagnosed with grade 1, 13.48% with grade 2, 8.61% with grade 3 and 34.83%

with grade 4 tumors. The rest of the patients (10.49%) were diagnosed with brain metastases.

Table 2. The grade of the studied tumors

Grade	Grade I	Grade II	Grade III	Grade IV	Meta
Number	87	36	23	93	28
Percent	32.58%	13.48%	8.61%	34.83%	10.49%

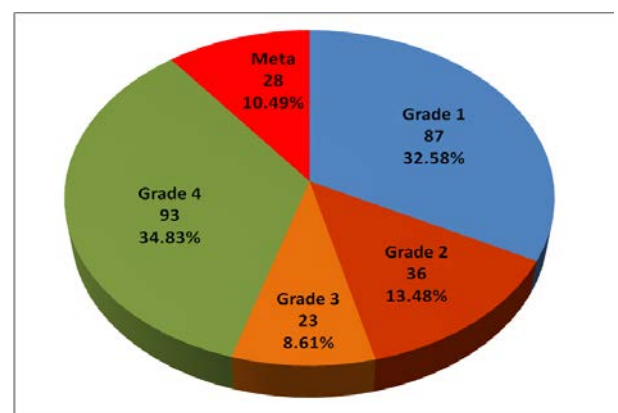


Fig.2. Grades of studied brain tumors

2. The correlations between brain tumor types or grades and age of the patients

Of the 267 patients studied, the mean average age was 52.36 years (SD 14.40 years). When we searched for correlations between tumor types and age of the patients we found that the corresponding p values resulted from the computing tests (Kruskal-Wallis, ANOVA) were both less than 0.001. This means that there is a high statistically significant difference between the mean values of the age found for each tumor type or between the ranks of those values.

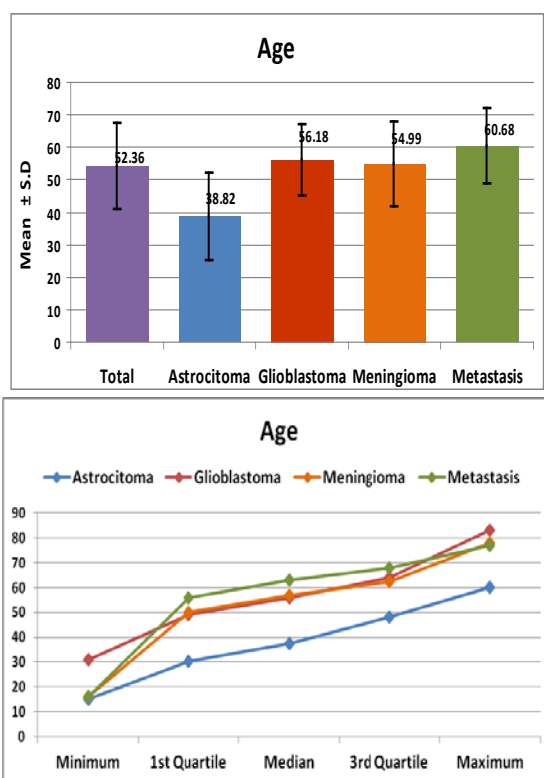


Fig.3. The correlation between brain tumors types and age of the patients

Because we found a statistical difference using the ANOVA test, we performed a post-hoc test to compare all the possible pairs of tumor types, in order to find any significant differences between any of them.

The Fisher LSD test showed highly significant differences between astrocitoma and metastasis, glioblastoma or meningioma and a significant difference between metastasis and meningioma.(Table 3)

Table 3. Age (post-hoc comparison of the means using Fisher LSD test following an ANOVA $p < 0.05$)

Comparison	p Fisher LSD	Significant
metastasis vs astrocitoma	< 0.0001	HS
metastasis vs meningioma	0.046	S
metastasis vs glioblastoma	0.121	NS
glioblastoma vs astrocitoma	< 0.0001	HS
glioblastoma vs meningioma	0.532	NS
meningioma vs astrocitoma	< 0.0001	HS

In our study astrocytomas affected the youngest group of patients (median age 37.5 years, mean $38,8 \pm 13.3$ years). Brain metastases were found in the oldest group of patients (median age 63 years, mean 60.6 ± 11 years). Glioblastomas (mean age 56 years) and meningiomas (mean age 57 years) were characterized by a similar age distribution.

We considered also important to determine the correlation between tumor grades and age of the patients. We found a high statistically significant difference between the mean values of the age found for each tumor grading and between the ranks of those values($p < 0.01$). (Fig.4)

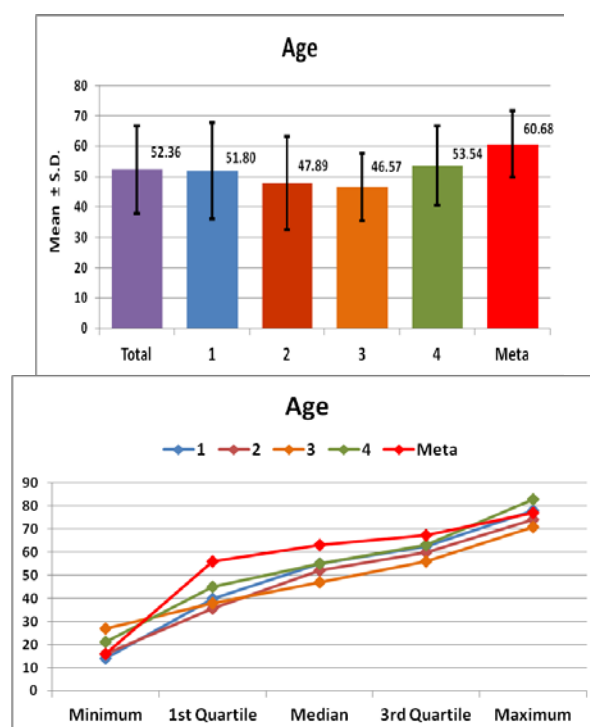


Fig.4. The correlation between brain tumors grade and age of the patients

Table 4. Age (post-hoc comparison of the means using Fisher LSD test following a n ANOVA $p < 0.05$)

Comparison	p Fisher LSD	Significant
Meta vs Grade3	0.000	HS
Meta vs Grade2	0.000	HS
Meta vs Grade1	0.004	HS
Meta vs Grade4	0.019	S
Grade 4 vs Grade3	0.034	S
Grade 4 vs Grade2	0.041	S
Grade 4 vs Grade1	0.408	NS
Grade 1 vs Grade3	0.112	NS
Grade 1 vs Grade2	0.160	NS
Grade 2 vs Grade3	0.724	NS

The Fisher LSD test showed highly significant differences between cerebral metastasis and grade 1, grade 2 or grade 3 tumors. There are also significant differences between grade 4 tumors and brain metastasis, grade 2 or grade 3 tumors. (Table 4)

Grade 4 tumors were the oldest group of primary brain tumors (mean 53.5±13 years), followed by grade 1 tumors (mean 51,8±15.9 years) , grade 2 (mean 47.9±15.3 years) and grade 3 tumors (mean 46.5±11.1 years).

3.The correlations between brain tumor types or grades and glycemia levels

First, we determined the plasma glycemia and we found that 47.94% of the 267 studied cases had high values of the plasma glucose. (Table 5)

Table 5. Values of plasma glycemia

	Glyc<105	Glyc>105	Total
Number	139	128	267
Percent	52.06%	47.94%	100.00%

Next, we considered important to determine the correlation between brain tumors types and glycemia. The corresponding p values resulted from computing the tests were both greater than 0.05. (Fig.5)

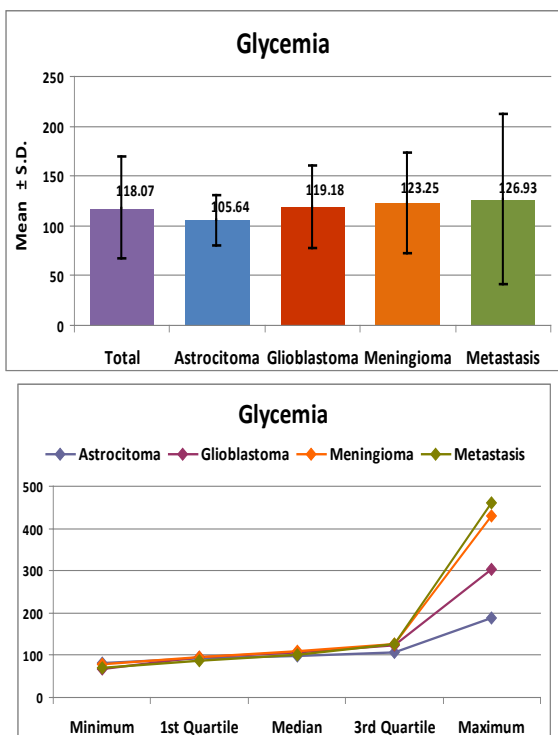


Fig.5. The correlation between brain tumors types and the values of glycemia

Therefore we decided to determine the correlation between the grade of the brain tumors and glycemia and we found that the corresponding p values were higher than the significance level.(p>0.05).

Although 47.94% of the 267 studied patients had values of plasma glycemia over 105mg/dl we found no statistical difference between the mean values of plasma glycemia in the various types (brain metastasis, astrocitoma, glioblastoma, meningioma) or grades of brain tumors (p>0.05). (Fig. 6)

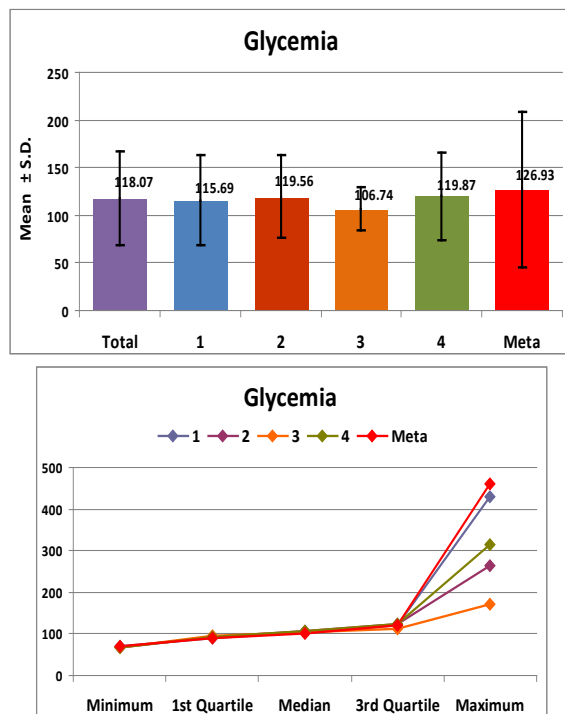


Fig.6. The correlation between brain tumors grade and the values of plasma glycemia

Because in both situations we found no globally statistical differences, we did not perform any post-hoc tests to compare all the possible pairs of tumor types or tumor grading.

4.The correlations between brain tumor types or grades and levels of plasma insulin

We also determined the insulin levels for the patients included in our study. Unexpectedly, we discovered that 57.68% of the 267 patients diagnosed with brain tumors had abnormal high levels of plasma insulin. (Table 6)

Table 6. Values of serum insulin

	Ins<25	Ins>25	Total
Number	113	154	267
Percent	42.32%	57.68%	100.00%

Therefore, we considered important to correlate the types of the studied brain tumors with the values of plasma insulin. As can be seen in Fig. 7, we observed that the mean values of insulin were the highest in metastatic brain tumors (43.36 μ IU/ml) followed by astrocytoma (42.76 μ IU/ml), while meningioma (31.75 μ IU/ml) and glioblastoma (31.49 μ IU/ml) patients had lower plasma levels of insulin. Kruskal-Wallis test ($p=0.277$) showed that there is no global significant difference between the ranks of the values, so the studied groups could be part of the same statistical population. (Fig.7) However, ANOVA test ($p=0.013$) suggested that there may be a statistically significant difference between the mean values of different subgroups of brain tumors.

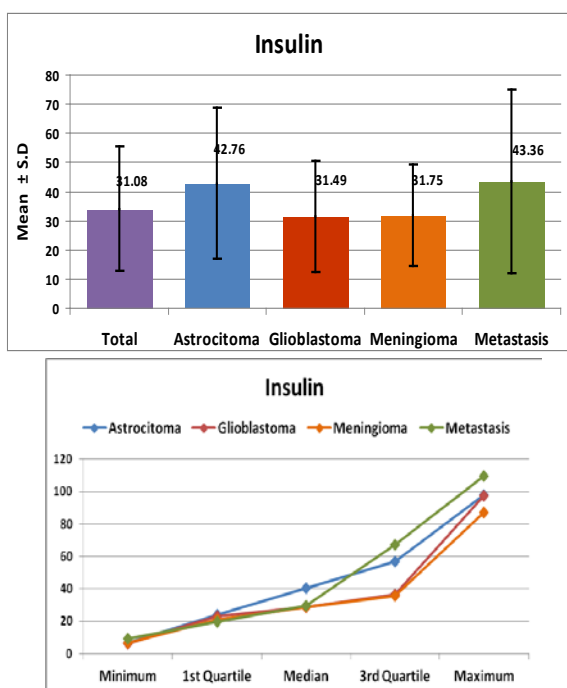


Fig.7. The correlation between brain tumor types and values of plasma insulin

We performed post-hoc tests to compare all the possible pairs of tumor types, in order to find significant differences between any of them. The Fisher LSD test showed significant differences between metastasis and glioblastoma or meningioma and between astrocytoma and glioblastoma or meningioma.(Table 7)

Therefore we conclude that in our group of patients brain metastasis and astrocytomas have higher plasma insulin levels compared with meningiomas or glioblastomas and that these results have statistical significance.

Table 7. Insulin (post-hoc comparison of the means using Fisher LSD test following an ANOVA $p<0.05$)

Comparison	p Fisher LSD	Significant
metastasis vs glioblastoma	0.014	S
metastasis vs meningioma	0.014	S
metastasis vs astrocitoma	0.922	NS
astrocitoma vs glioblastoma	0.028	S
astrocitoma vs meningioma	0.029	S
meningioma vs glioblastoma	0.936	NS

After that we analyzed a possible correlation between the grade of brain tumors and the value of plasma insulin using the same tests. As it can be seen in Fig. 8 the mean values of insulin were the highest in metastatic brain tumors (43.36 μ IU/ml) followed by grade 3 brain tumors (35.30 μ IU/ml). Grade 1, 4 and 2 brain tumors had lower mean values of plasma insulin: 30.25, 29.06 and 27.07 μ IU/ml respectively. We also discovered that there could be a statistically significant difference between the mean values of the insulin levels found for each tumor grading ($pANOVA=0.02$). but we found no significant difference between the ranks of the values(p KW=0.42). (Fig.8)

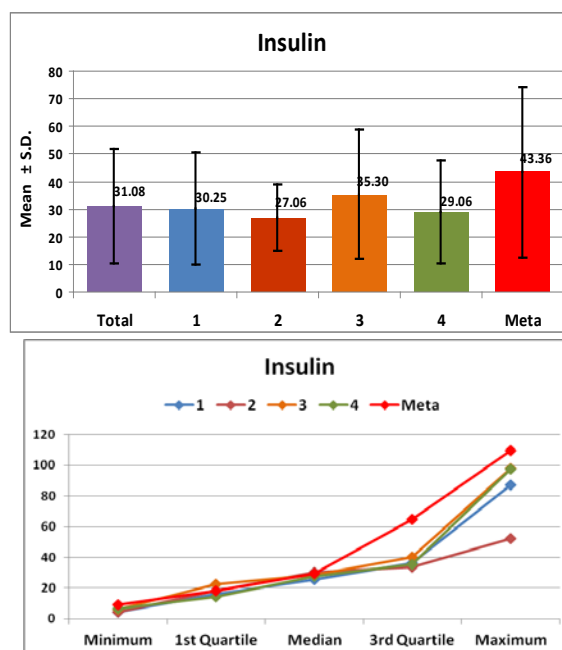


Fig.8. The correlation between brain tumors grades and the values of plasma insulin

In Table 8 it can be seen that we performed post-hoc tests to compare all the possible pairs

of tumor grading, in order to find the significant differences between any of them. The test showed significant differences between metastasis and tumoral grades 1, 2 and 4.

Table 8. Insulin (post-hoc comparison of the means using Fisher LSD test following an ANOVA $p < 0.05$)

Comparison	p Fisher LSD	Significant
Meta vs Grade 2	0.004	HS
Meta vs Grade 4	0.004	HS
Meta vs Grade 1	0.008	HS
Meta vs Grade 3	0.241	NS
Grade 3 vs Grade 2	0.134	NS
Grade 3 vs Grade 4	0.193	NS
Grade 3 vs Grade 1	0.295	NS
Grade 1 vs Grade 2	0.435	NS
Grade 1 vs Grade 4	0.699	NS
Grade 4 vs Grade 2	0.621	NS

Therefore we can conclude that in our group of patients metastasis and grade 3 brain tumors have higher levels of plasma insulin compared with grade 1, 2 and 4 brain tumors. The

statistical difference between the mean values of plasma insulin is highly significant between metastasis and grade 1, 2 and 4 brain tumors while the comparison between the other types of brain tumors has no statistical significance.

Trying to find possible correlations in the group of primary CNS tumors, we decided to correlate the values of plasma insulin with the tissue of origin of the brain tumors. The main groups were represented by tumors with neuroepithelial origin (n=128), meningeal origin (n=101) and others (n=10). As it can be seen in Fig. 9 the mean values of plasma insulin were higher in neuroepithelial tumors (30.84 μ IU/ml) compared with meningeal tumors (29.99 μ IU/ml) but these results are not statistically significant. (Table 9)

Although the group of other brain tumors showed statistical differences when compared with neuroepithelial and meningeal tumors, we didn't take into account these findings due to the heterogeneity of this group and the small number of patients that it contains.

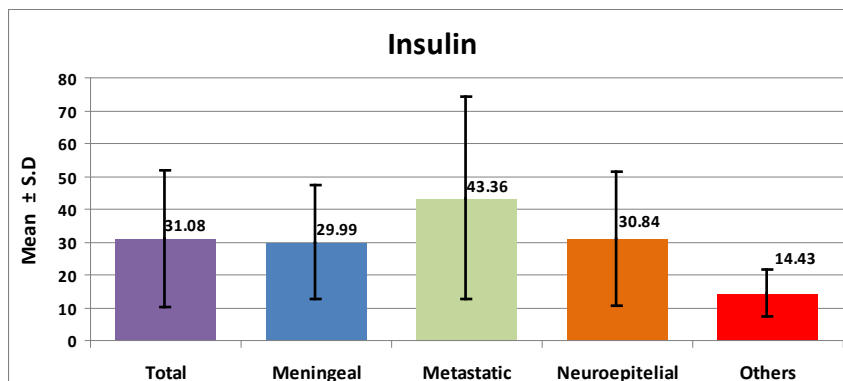


Fig.9. The correlation between brain tumors origin tissue and the values of plasma insulin

Table 9: Insulin (post-hoc comparison of the means using Fisher LSD test following an ANOVA $p < 0,05$)

Comparison	p Fisher LSD	Significance
metastatic vs other	0.000	HS
metastatic vs meningeal	0.006	S
metastatic vs neuroepithelial	0.009	S
neuroepithelial vs other	0.015	S
neuroepithelial vs meningeal	0.755	NS
meningeal vs other	0.022	S

Discussion

This study is one of a few that focuses on the correlations between glucose levels, insulin levels and various types and grades of brain tumors. In the present study, we investigated 267 patients with different type of brain tumors: 32.96% were diagnosed with meningiomas, 29.21% with glioblastomas, 10.49% with metastasis and 8.24% were diagnosed with astrocytomas. The other 19.85% had: schwannoma, meduloblastoma, meningeal sarcoma, ependimoma, oligodendroglioma, hemangiopericitoma, and so on.

CBTRUS (Central Brain Tumor Registry of the United States) recently reported that between 2006 and 2009 the distribution of the

primary CNS tumors by histology in a number of 311,202 patients was: 35.5% meningiomas, 15.8% glioblastomas, 6.3% astrocytomas. The rest of the patients were diagnosed with: ependymal tumors (2.0%), oligodendrogliomas (1.8%), embryonal tumors (1.2%), pituitary tumors (14.1%), craniopharyngioma (0.9%), lymphoma (2.2%), nerve sheath tumors (8.3%), germ cell tumors (0.15%) and other (11.5%). The incidence of brain metastases is not accurately known. However there are some epidemiological studies that report the incidence of brain metastases to be equal or no more than twice that of gliomas.[20]

Comparing the data from the literature and our results seems that our population of brain tumor patients had similar histological characteristics as the data already published. Only glioblastomas were almost twice as frequent in our statistics (29.21%), probably because our data came from a neurosurgery clinic and not from general population.

It is already known that brain tumors WHO grading system is a malignancy scale which is based on the histologic features of the tumors. The histologic grades are from WHO grade I which includes tumors with low proliferative potential to WHO grade IV which includes tumors with rapid preoperative and postoperative progression and fatal outcome.[19] In our population 32.58% of the patients had grade I tumors, 13.48% grade II tumors, 8.61% grade III tumors and 34.83% had grade IV tumors. Until now there are no published epidemiologic data of the WHO grades of the brain tumors.

The mean age of the patients diagnosed with astrocytomas, was the lowest when compared with meningioma, glioblastoma and brain metastasis patients. The difference was statistically significant. When compared the tumors by their WHO grades we found significant differences between metastasis and grade I, II or III tumors and also between grade IV tumors and metastasis or grade II or III tumors. The group of brain metastases and that of grade 4 tumors have the highest age in our statistic. All these results are in correspondence with the already published data. [21-23]

It is worth to notice that in our group of patients the median age was 55 years compared with 59 years in the last CBTRUS report. The means for astrocytomas were 37.5 years (between 48 and 54 years in CBTRUS), glioblastomas 56 years (64 years CBTRUS) and meningiomas 57 years (65 years CBTRUS).

It is already well known that carcinogenesis is a very complex multifactorial process which in part is influenced by the metabolic disturbances.[24] An important component of the metabolic syndrome is hyperglycemia. Glucose is the major substrate for brain metabolism. Under normal physiological conditions the adult brain develops his energy from the aerobic oxidation of the glucose. When the blood glucose levels are reduced the mature brain will metabolize ketone bodies for energy. In contrast, brain tumors are dependent only on glucose for energy, and high-grade brain tumors consume even more glucose.[25] Some studies describe correlations between glucose level and the neoplastic transformation of the cells however most of the results of the studies are inconclusive.[26] Therefore we considered important the hypothesis that maybe hyperglycemia itself promotes tumor growth. Although 47.94% of the 267 studied patients had values of the plasma glycemia over 105mg/dl, in our study we did not find correlations between brain tumor types or grades and values of plasma glycemia. We can conclude that in our group of patients glycemia does not necessarily mediate the relationship with the brain tumors.

McGirth et al. found that persistent hyperglycemia is an independent factor associated with decreased survival in a group of 367 patients with malignant astrocytomas (grade III and IV). He considered the values of blood glucose higher than 180mg/dl as being hyperglycemic and found in his group in the first three months after surgery 19% patients with isolated hyperglycemia and 8% patients with persistent hyperglycemia. The survival of persistent hyperglycemic patients was 5 months versus 11 months in patients with normal glycemia.[27]

It is important to remark that 47.94% of the patients had levels of plasma glucose over 105mg/dl which may display an abnormal activity of insulin. It can be explained either through abnormal glucose tolerance or insulin resistance (followed by compensatory hyperinsulinemia), or less insulin secretion.[28] As it is known that insulin is involved in the differentiation of the cells, an abnormal activity of the insulin may indicate a greater risk of undifferentiated growth of the cancer cells.[29]

Hyperinsulinemia is also related to the metabolic syndrome. Although, the condition is often associated with type 2 diabetes, it is not the cause of the disease but only one symptom. Hyperinsulinemia has been already linked with

various cancers like: breast, endometrial and prostate cancer.(16-18) First, we discovered that 57.68 % of the 267 brain tumors patients that we studied had high levels of plasma insulin (over 25 μ U/ml) Therefore we determined the correlations between brain tumors types and the values of plasma insulin.. We found that brain metastasis and astrocytomas have higher plasma insulin levels compared with meningiomas and glioblastomas. These results were statistical significant. When we studied the values of plasma insulin referred to brain tumor grades we found that metastasis and grade 3 brain tumors have higher levels of plasma insulin compared with grade 1, 2 and 4 brain tumors. The statistical difference between the mean values of plasma insulin is highly significant between metastasis and grade 1, 2 and 4 brain tumors while the comparison between the other types of brain tumors has no statistical significance.

Next , we tried to find a correlation between the values of plasma insulin and the tissue of origin of the brain tumors. We found that the neuroepithelial brain tumors had higher levels of plasma insulin compared with meningeal tumors, but the result is not statistically significant.

This is the first study that demonstrates that patients with brain metastasis and grade 3 brain tumors have higher levels of plasma insulin compared with other brain tumors The hormone stimulates proliferation process by increasing IGF-1 production and bioavailability. [30] IGF-1 promotes the proliferation and angiogenesis and inhibits apoptosis.[31] The IGF receptors, mainly IGF-1R, are known to be overexpressed in many cancer cells included brain tumors.[32] IGF-1R is crucial for tumor transformation and survival of the tumor cell through the activation of some intracellular pathways like: p21ras/MAPK or PI3K/AKT. [31, 33] It is also already known that high concentrations of IGF-1 is more likely correlated with the risk of low-grade gliomas than high-grade gliomas and meningiomas.[34, 35] Our results also correlated increased circulating insulin levels with metastasis and astrocytomas.

Our findings rises the question whether the management of hyperglycemia and hyperinsulinemia would lead to an improvement in the survival, quality of life and provide new treatment options for patients with brain tumors.

In this study, we found no correlation between the plasma glycemia and brain tumor types or grades. We also found that the mean values of plasma insulin were higher in brain

metastasis and astrocytomas and the results were statistically significant when compared with other types of brain tumors. Finally, found that the expression of this peptide was higher in metastasis and grade 3 brain tumors with statistically significant results.

One limitation of our study that must be highlighted is that we measured only the baseline levels of glycemia and serum insulin. Maybe repeated measurements could bring more data about the evolution of these biomarkers in brain tumors. One of the reasons why we didn't follow up these patients was that they were submitted to surgery and received corticotherapy for variable intervals of time.

Conclusions

Our data demonstrate for the first time that patients with astrocytomas have high levels of plasma insulin while patients with other types of brain tumors (meningiomas and glioblastomas) have lower levels of the peptide. We also find that brain metastasis and grade 3 brain tumors have higher levels of plasma insulin compared to the grade 1, 2 and 4 brain tumors.

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