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Association of metabolic syndrome with glioblastoma: a retrospective cohort study and review

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Abstract

Background. Metabolic syndrome is identified as a risk factor for the development of several systemic cancers, but its frequency among patients with glioblastoma and its association with clinical outcomes have yet to be determined. The aim of this study was to investigate metabolic syndrome as a risk factor for and affecting survival in glioblastoma patients.

Methods. A retrospective cohort study, consisting of patients with diagnoses at a single institution between 2007 and 2013, was conducted. Clinical records were reviewed, and clinical and laboratory data pertaining to 5 metabolic criteria were extrapolated. Overall survival was determined by time from initial surgical diagnosis to date of death or last follow-up.

Results. The frequency of metabolic syndrome among patients diagnosed with glioblastoma was slightly greater than the frequency of metabolic syndrome among the general population. Within a subset of patients ($n = 91$) receiving the full schedule of concurrent radiation and temozolomide and adjuvant temozolomide, median overall survival was significantly shorter for patients with metabolic syndrome compared with those without. In addition, the presence of all 5 elements of the metabolic syndrome resulted in significantly decreased median survival in these patients.

Conclusions. We identified the metabolic syndrome at a slightly higher frequency in patients with diagnosed glioblastoma compared with the general population. In addition, metabolic syndrome with each of its individual components is associated with an overall worse prognosis in patients receiving the standard schedule of radiation and temozolomide after adjustment for age.

Keywords

glioblastoma | hyperglycemia | metabolic syndrome | obesity | survival

Metabolic syndrome (MetS) is a well-established risk factor for nonneoplastic disorders such as type 2 diabetes mellitus and atherosclerotic cardiovascular disease.[1] It is also identified as a risk factor for systemic cancers, notably breast and prostate cancer.[2–5] In addition, there is evidence that MetS is associated with a more aggressive tumor biology and worse outcome in systemic cancers.[6,7] The frequency of MetS and the association of MetS with clinical outcome in glioblastoma (GBM) patients have not yet been determined. We retrospectively reviewed the clinical and outcome data of newly diagnosed GBM (nGBM) adult patients at our center to determine the frequency of MetS and to compare the clinical outcome of patients with and without MetS.

Methods

We retrospectively reviewed the clinical records of all patients (N = 146) with nGBM at University Hospitals Cleveland Medical Center (UHCMC) Seidman Cancer Center from 2007 to 2013 enrolled in the Ohio Brain Tumor Study, an institutional review board–approved clinical and tissue procurement study, with data updated through 2016.[8] Clinical and laboratory criteria for the diagnosis of MetS were based on the consensus report by Alberti et al[1] and included ≥3 of the following: hyperglycemia, hypertension, elevated triglycerides, reduced high-density lipoprotein C, and obesity. The criteria are identified as follows: for patients in whom fasting blood sugar levels were not available, hyperglycemia was determined by a history of diabetes and/or drug treatment of elevated glucose. Hypertension was determined by systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg or drug treatment for hypertension and a history of hypertension. Hyperlipidemia was identified by elevated triglycerides (≥150 mg/dL) and reduced high-density lipoprotein C (HDLC) (<40 mg/dL in males, <50 mg/dL in females) or drug treatment for elevated triglycerides or reduced HDLC. The criteria include a definition of obesity based on waist circumference which was not available in the medical records, and we substituted body mass index (BMI) ≥30 kg/m^2, which is an accurate surrogate for waist circumference.[9–11] Criteria were obtained prior to the diagnosis of GBM and the administration of steroids. Time to progression (TTP) and overall survival (OS) were determined by the interval from initial surgical diagnosis to imaging progression and to date of death or last follow-up.

Characteristics of nGBM patients with and without MetS were compared using chi-square tests or Fisher's exact test for categorical variables. Differences in age were compared using t-tests, and Karnofsky performance status (KPS) scores were compared using the Wilcoxon rank sum test. Kaplan–Meier OS analysis stratified by MetS status (and by individual MetS factors) was performed generating median OS times, in months, with 95% CIs and log-rank tests, overall and for those who received standard therapy (surgery plus concurrent radiation and temozolomide and adjuvant temozolomide). In addition, adjusted median OS times with 95% CIs were generated, adjusting for age at diagnosis. Statistical significance was set at a P-value of 0.05.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the institutional review board at our institution. Informed consent was obtained from all participants.

Results

Table 1 shows the clinical characteristics, including prognostic factors of age, postoperative KPS, degree of resection, isocitrate dehydrogenase (IDH) mutational status, O^6-methylguanine-DNA methyltransferase (MGMT) methylation, and treatment with radiation or radiation and temozolomide. Temozolomide was administered by the Stupp and Weber standard regimen.[12] MetS was identified in 52 out of 146 total patients (35.6%), 38 men and 14 women. The median age in patients with MetS was not significantly different than that of patients without MetS (66.2 and 63.1 y, respectively, P = 0.1391).

Median OS in the study population was 11.3 months (95% CI = 9.3–12.8). Although the difference in median OS was not statistically significant in those with MetS compared with those without MetS, there was a trend toward decreased survival in those with MetS (7.7 mo [95% CI = 5.9–12.4]) compared with those without MetS (12.7 mo [95% CI = 10.8–16.9]) (log rank P = 0.224) (Fig. 1). An analysis was conducted of the subset of patients that received the full schedule of radiation and concurrent and adjuvant temozolomide (n = 91; 61.1% of all patients) using a Cox proportional hazards model adjusted for age at diagnosis. Median OS was significantly shorter for those with MetS (12.4 mo, 95% CI = 9.5–14.2) versus those without MetS (17.9 mo, 95% CI = 15.0–22.1) (log-rank P = 0.18) (Fig. 2). When survival models were additionally adjusted for whether patients underwent gross total resection, this factor was associated with decreased hazard of death but was not statistically significant (P = 0.62). The number of tumor tissues studied for MGMT methylation and IDH mutation was small and we were thus unable to analyze those as factors in outcome. There was no significant association between MetS and TTP (median TTP was 11.8 mo in those with MetS and 11.0 mo in those without) or between individual elements of MetS with TTP (Table 1).

Table 1 shows the frequency of individual MetS elements and other prognostic variables. Though MetS data were not routinely assessed at clinic visits, very few MetS data elements were missing from electronic health records. The most common element of MetS we identified was hypertension (63.0% of patient population). Within the subset of patients receiving standard of care and adjusted for age at diagnosis, the presence of all 5 MetS criteria resulted in significantly decreased median OS (Table 2).

Table 1 Characteristics of nGBM patients with and without metabolic syndrome

	Overall		With MetS		Without MetS		*P*-value[a]
	N = 146	%	*n* = 52	%	*n* = 94	%	
Treatment groups							0.1983[b]
Surgery only	31	21.2	14	26.9	17	18.1	
Surgery + radiation only	23	15.8	6	11.5	17	18.1	
Surgery, concurrent radiation + temozolomide	18	12.3	9	17.3	9	9.6	
Surgery, concurrent radiation + temozolomide, and adjuvant temozolomide	73	50.0	23	44.2	50	53.2	
Extent of resection							0.5324
Biopsy	11	7.5	5	9.6	6	6.4	
Subtotal resection	62	42.5	24	46.2	38	40.4	
Gross total resection	73	50.0	23	44.2	50	53.2	
Sex							0.1859
Male	89	61.0	38	73.1	51	54.3	
Female	57	39.0	14	26.9	43	45.7	
Race							0.2668
White	134	91.8	49	94.2	85	90.4	
Nonwhite	12	8.2	3	5.8	9	9.6	
IDH1/2 mutation							0.1899[b]
Wild type	43	29.5	15	28.8	28	29.9	
Mutant	6	4.1	4	7.7	2	2.1	
Not tested	97	66.4	33	63.5	64	68.0	
MGMT promoter methylation							1.0000 [b]
Methylated	19	13.0	7	13.5	12	12.8	
Unmethylated	16	11.0	5	9.6	11	11.7	
Not tested	109	74.7	40	76.9	69	73.4	
Elevated blood sugar							5.68×10^{-10}
Elevated	40	27.4	30	58.8	10	10.6	
Not elevated	105	71.9	21	41.2	84	89.4	
Missing data	1	0.6	–	–	–	–	
Hypertension							1.21×10^{-8} [b]
Hypertensive	92	63.0	48	92.3	44	46.8	
Not hypertensive	54	37.0	4	7.7	50	53.2	
Missing data	0	0.0	–	–	–	–	
Triglycerides							4.95×10^{-17}
Increased triglycerides	52	35.6	42	80.8	10	10.9	
Triglycerides not increased	92	63.0	10	19.2	82	89.1	
Missing data	2	1.4	–	–	–	–	
HDLC							2.10×10^{-17}
Decreased HDLC	57	39.0	44	88.0	13	14.4	
No decreased HDLC	83	56.8	6	12.0	77	85.6	
Missing data	6	4.1	–	–	–	–	
Obesity							4.17×10^{-6}
Obese	44	30.1	28	53.8	16	17.0	
Not obese	101	69.2	24	46.2	77	81.9	
Missing data	1	0.7	–	–	1	0.1	
Age, y, mean	64.2		66.2		63.1		0.1391
Postoperative KPS (median)	70		70		70		0.1687[c]

Table 1 Continued

Median survival, mo (95% CI)	11.3 (9.3–12.8)	7.7 (5.9–12.4)	12.70 (10.8–16.9)	0.224
Median survival [surgery, radiation + temozolomide only, adjusted for age], mo (95% CI)	14.0 (12.8–19.7)	12.4 (9.5–14.2)	17.9 (15.0–22.1)	0.1847[d]
Median TTP, mo (95% CI)	11.0 (10.0–13.4)	11.8 (8–..)	11.0 (10.0–13.4)	0.347
Median TTP [surgery, radiation + temozolomide only, adjusted for age], mo (95% CI)	10.3 (8.6–13.4)	10.3 (8.0–..)	11.0 (9.3–13.4)	0.7000 [d]

[a]Test of significance between MetS groups.
[b]Fisher's exact test.
[c]Wilcoxon rank sum test.
[d]*P*-value for trait in Cox proportional hazards model adjusted for age at diagnosis.
**Confidence interval (CI) cannot be calculated.

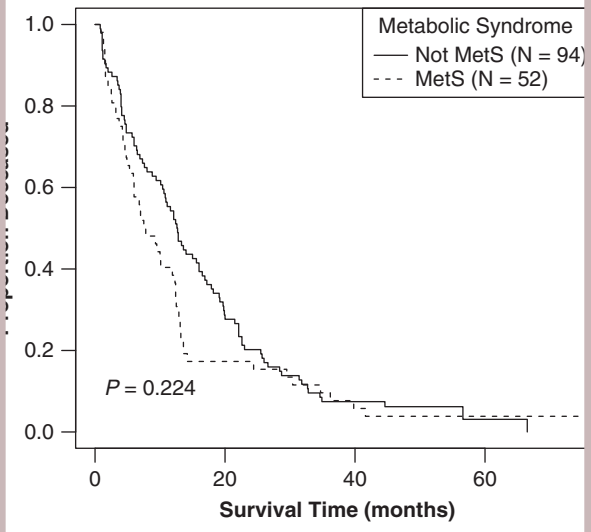

Fig. 1 Overall survival time based upon MetS status. Kaplan–Meier curve stratified by MetS status depicts that OS time, in months, did not vary significantly based upon MetS status (median OS for patients with MetS = 7.7 mo, 95% CI: 5.9–12.4, vs median OS in patients without MetS = 12.7 mo, 95% CI: 10.8–16.9, log rank *P* = 0.22).

Discussion

A variety of criteria to diagnose MetS are proposed. We used the criteria recommended by the multidisciplinary task force of Alberti and colleagues,[1] except that we used BMI (patient weight divided by height) as a surrogate measure of obesity because waist circumference data were not available. We required that MetS elements be identified prior to the diagnosis of GBM because nGBM patients are typically treated pre- and postoperatively with a corticosteroid to reduce vasogenic edema. Corticosteroids can increase blood pressure, serum glucose, and, over time, BMI, resulting in a patient meeting diagnostic criteria that are due to an extrinsic pharmacologic effect.

In this retrospective review, the frequency of MetS in nGBM patients was 35.6%, slightly greater than the national prevalence of 34.2% as documented based on an analysis of NHANES (National Health and Nutrition Examination Survey) data from 2007–2012.[13] However, our study was conducted in Ohio, which has a slightly higher prevalence of diabetes (in 2013, Ohio = 10.4% vs US = 9.7%), of overweight or obesity (in 2013, Ohio = 65.1% vs US = 64.3%), and of hypertension (in 2013, Ohio = 33.5% vs US = 31.4%).[14]

No other published report details the frequency of MetS and its impact on survival in GBM, though individual elements of MetS in relation to the development of GBM have been studied by others. Obesity in particular has been studied as a potential risk factor in glioma development. Several meta-analyses have produced conflicting results. Selected studies included in these meta-analyses are summarized in Table 3. Niedermaier and colleagues conducted a systematic review and meta-analysis of adiposity and physical activity and their relation to glioma.[15] Elevated BMI was not found to be associated with increased risk of glioma. Sergentanis and colleagues reported that while elevated BMI was associated with an increased risk of glioma in females, the relationship was not statistically significant in males.[16] Dai and colleagues determined that obesity was an overall risk factor in the development of glioma,[17] whereas in a large prospective study by Wiedemann obesity was not associated with risk for development of any glioma subtype.[18]

Hyperglycemia, hypertension, and dyslipidemia have also been studied as individual risk factors for glioma. Two retrospective case-control studies found no association between diabetes, hyperlipidemia, and risk for developing GBM.[19,20] Another case-control study found an inverse association between long-term diabetes, chronic hyperglycemia, and glioma risk.[21] Differing results were found in a prospective study conducted by Edlinger and colleagues that included 580 000 individuals, 1312 of whom had diagnoses of primary brain tumor over the course of 10 years.[22] Increased diastolic blood pressure and triglycerides were found to be associated with increased risk of brain tumor, including high-grade glioma. An additional case-control study found a significantly higher prevalence of hypertension in glioma patients age 60 years and older compared with all other cancer patients.[23]

Individual elements of MetS in relation to clinical outcome and survival in patients with nGBM have been reported by others. Jones and colleagues prospectively studied the effect of BMI on mortality in 1259 patients with untreated GBM using self-reported height and weight or data abstracted from medical records to calculate BMI.[24] There was no significant association between BMI and survival in nGBM patients. However, in a retrospective study of patients surgically treated for high-grade glioma, Chambless and colleagues found elevated BMI to be an independent risk factor for poor outcome.[25] More recently, Siegel and colleagues identified pre-diagnostic obesity, defined as the presence of elevated BMI 1 to 5 years prior to diagnosis, as a significant independent predictor of poor outcome among high-grade glioma patients.[26] A literature review by Barami found obesity to be associated with decreased OS in patients with GBM diagnosis.[19] In our age-adjusted analysis of patients receiving standard therapy of concurrent radiation and temozolomide and adjuvant temozolomide, obesity was associated with lower median survival (12.9 mo in obese patients vs 15 mo in non-obese patients), though not statistically significant ($P = 0.18$).

Hyperglycemia was assessed in several retrospective studies, all of which confirmed worse survival in malignant glioma patients with persistent hyperglycemia after controlling for glucocorticoid dose and other confounding factors.[27–29] However, a limitation of each of these studies is the use of random blood glucose to define hyperglycemia (not fasting levels or glycated hemoglobin levels). In addition, the degree of tumor resection was not assessed as a prognostic variable. A meta-analysis of published studies through January 2018 also concluded that hyperglycemia conferred a statistically significant poorer OS in patients with nGBM.[30] Our study also found a significant correlation of hyperglycemia with decreased median OS in those

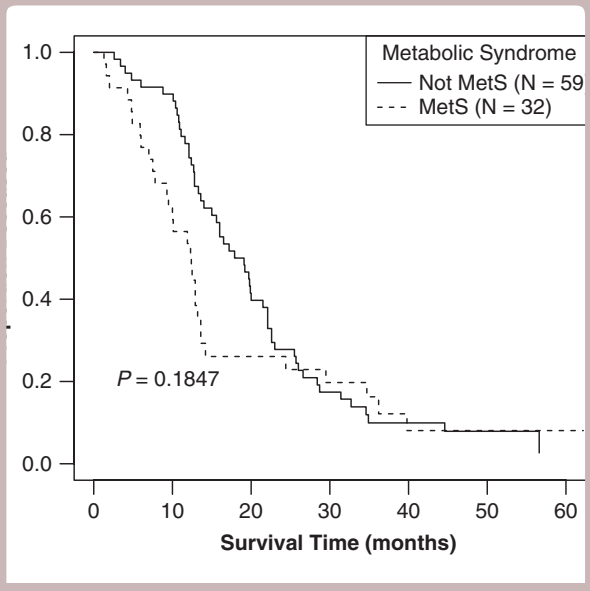

Fig. 2 Age-adjusted survival status for patients receiving concurrent radiation and temozolomide ($N = 91$). A Kaplan–Meier curve stratified by MetS status and adjusted for age at diagnosis depicts OS status, in months, for patients receiving concurrent radiation and temozolomide and adjuvant temozolomide. Patients with MetS had a significantly shorter median OS (12.4 mo, 95% CI: 9.5–14.2) compared with patients without MetS (17.9 mo, 95% CI: 15.0–22.1, $P = 0.18$).

Table 2 Frequency of nGBM patient population with metabolic syndrome factors ($N = 146$) and correlation of MetS diagnostic criteria with OS in patients with and without nGBM

	All Individuals			Individuals Who Received Surgery, Concurrent Radiation, and Temozolomide		
	N	Median survival, mo (adjusted for age) (95% CI)	*P* value[a]	N	Median survival, mo (adjusted for age) (95% CI)	*P*-value[a]
Elevated blood sugar						
Elevated blood sugar	40	7.2 (4.3–12.4)	0.0976	23	11.9 (9.3–14.2)	0.0298
Blood sugar not elevated	105	12.6 (10.4–15.6)		67	17.2 (13.6–22.1)	
Hypertension						
Hypertensive	92	7.4 (5.9–11.1)	0.001	49	12.9 (11.9–15.6)	0.1945
Not hypertensive	54	18.2 (13.6–22.1)		42	19.7 (16.0–23.0)	
Triglycerides						
Increased triglycerides	52	7.0 (5.3–12.4)	0.0640	31	12.4 (9.3–14.2)	0.0945
Triglycerides not increased	92	12.9 (11.1–16.9)		59	17.9 (14.0–22.1)	
HDLC						
Decreased HDLC	57	9.4 (6.0–12.9)	0.8840	33	13.2 (12.4–25.7)	0.9633
No decreased HDLC	83	12.4 (10.4–16.0)		54	16.0 (13.3–19.9)	
Obesity						
Obese	44	11.5 (7.8–13.6)	0.7600	30	12.9 (11.1–19.7)	0.1763
Not obese	101	11.6 (7.5–13.3)		60	15.0 (12.8–22.1)	

[a] *P*-value for trait in Cox proportional hazards model adjusted for age at diagnosis.

Table 3 A review of selected studies and meta-analyses examining obesity as a risk factor for the development of GBM

Reference	Study Location and Time	Subjects	Risk Estimate (95% CI)	Included in Dai et al[15]?	Included in Niedermaier et al[31]?	Included in Sergentanis et al[34]?
Benson et al (2008)[33]	United Kingdom 1996–2001	*N* = 646 women with diagnosis of glioma and 1 249 670 population controls	1.07 (0.84–1.34)[1]	X	X	X
Cabaniols et al (2011)[34]	France 2005	*N* = 122 men and women with diagnosis of glioma and 122 hospital controls	0.70 (0.41–1.18)[2]		X	X
Edlinger et al (2012)[28]	Sweden, Austria, and Norway 1972–2006	*N* = 436 men and women with diagnosis of high-grade glioma and 580 000 population controls	1.03 (0.85–1.26)[3]			X
Jones et al (2010)[29]	United States, 1991–2008	*N* = 1259 men and women with diagnosis of glioblastoma multiforme	1.08 (0.91 –1.28)[3]	X		
Little et al (2013)[35]	United States 2004–2012	*N* = 1111 men and women with diagnosis of glioma and 1096 community controls	1.06 (0.70–1.60)[2]			X
Michaud et al (2011)[36]	Europe 1992–2000	*N* = 340 men and women with diagnosis of glioma and 380 775 community controls	1.06 (0.76–1.48)[3]	X	X	X
Moore et al (2009)[37]	United States 1995–2003	*N* = 257 men and women with diagnosis of glioma and 305 681 controls	1.29 (0.89–1.86)[1]	X	X	X
Siegel et al (2003)[16]	United States 2005–2012	*N* = 853 men and women with diagnosis of high-grade glioma	1.24 (1.00–1.54)[3]	X		
Wiedmann et al (2017)[38]	Norway 1984–2008	*N* = 148 men and women with diagnosis of glioma and 74 242 population controls	1.04 (0.58–1.85)[3]	X		X

[1]RR, relative risk; [2]OR, odds ratio; [3]HR, hazard ratio.

patients receiving standard of care (11.9 mo in patients with elevated blood sugar vs 17.2 mo in patients without elevated blood sugar, $P = 0.03$).

Our study is the first to analyze hypertension and dyslipidemia as potential prognostic factors for survival in nGBM patients. We found an association between hypertension and decreased median survival in patients receiving standard radiation and temozolomide (12.9 mo in hypertensive patients vs 19.7 mo in nonhypertensive patients, $P = 0.19$). We also found an association between dyslipidemia and decreased median survival (12.4 mo in patients with elevated triglycerides vs 17.9 mo in patients without elevated triglycerides, $P = 0.09$ and 13.2 months in patients with decreased HDLC vs 16 mo in patients without decreased HDLC, $P = 0.96$). These data should be interpreted with caution as laboratory values of lipids were not routinely available and dyslipidemia in many patients was determined by prescribed medications, which may have been prescribed prophylactically.

A study of the association between MetS and GBM is clinically relevant because it may increase our understanding of the pathophysiology of GBM development. Human glial tumors possess insulin receptors with insulin-binding activities. Insulin has been shown to stimulate glucose uptake in cultures of human GBM cells.[31] Thus, there is a rationale to suggest that insulin resistance, one characteristic of MetS, may be a factor in the growth of gliomas. Alternatively, hyperglycemia alone may promote tumor growth. Although we are not certain if MetS is more prevalent among nGBM patients compared with the general population, we did identify that individual criteria of MetS significantly affected survival in nGBM patients who received standard radiation and temozolomide and that the combination of all MetS factors carries an especially poor prognosis. Other potential mechanisms by which metabolic abnormalities might influence GBM outcome include the effects of obesity on the tumor microenvironment, including the increased levels and availability of growth factors such as insulin and insulin-like growth factor, altered adipocytokine levels, low-grade inflammation, and oxidative stress.[32]

The retrospective design is a limitation in our study because not all elements of MetS were routinely obtained at clinic visits. We extrapolated data on the use of antihypertensives and lipid-lowering agents as treatment for hypertension and hyperlipidemia, whereas these may have been used in a prophylactic fashion. However, the study design did allow us to include pretreatment BMI and glucose levels. In addition, we included patients who did not receive standard radiochemotherapy, typically because of low KPS or advanced age, and are thus representative of the typical nGBM population. To our knowledge, no prior studies have assessed the effect of hypertension

or dyslipidemia as factors affecting survival outcome in patients with nGBM; it merits further investigation in a prospective study design. Because of small numbers of available tissue of MGMT methylation and IDH mutation status, we were not able to incorporate these variables into the outcome assessment.

Conclusions

Despite the limitations in our study, the association of MetS with a worse prognosis in GBM patients receiving standard radiation and temozolomide provides the rationale for a prospective study to determine clinical and laboratory evidence of MetS in nGBM compared with sex- and age-matched controls, and to correlate the individual factors of MetS with patient outcome. If MetS is found to impact treatment outcome, the potential exists that efforts to control MetS in nGBM patients could lead to improved survival by lifestyle changes and medications appropriate to the individual factors identified.

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Conflict of interest statement. The authors declare that they have no conflicts of interest or relevant financial relationships to disclose.

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