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PROGRAMA DE MAESTRIA Y DOCTORADO EN CIENCIAS MÉDICAS, ODONTOLOGICAS Y DE LA SALUD

EL FACTOR DE CRECIMIENTO HEPATOCÍTICO ESTÁ ASOCIADO CON POBRE PRONÓSTICO EN GLIOMAS MALIGNOS Y ES UN PREDICTOR DE RECURRENCIA DE MENINGIOMAS

PUBLICACIÓN DE PROTOCOLO

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PRESENTA

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ABREVIATURAS

HGF (des sus siglas en inglés): factor de crecimiento hepatocítico.

AA: astrocitomas anaplásicos.

GM: glioblastomas multiformes.

VEGF: factor de crecimiento del endotelio vascular.

PDGF (des sus siglas en inglés): factor de crecimiento derivado de plaquetas.

FGF (des sus siglas en inglés): factor de crecimiento de fibroblastos.

I. RESUMEN DEL TRABAJO

Introducción

El factor de crecimiento hepatocítico (HGF, de sus siglas en inglés) es una citosina participante en múltiples funciones celulares, promoviendo la proliferación, motilidad y morfogénesis de las células epiteliales. Algunos tumores malignos, como el carcinoma mamario, broncogénico y el mieloma múltiple, sobre-expresan HGF y su receptor. HGF también está presente en astrocitos normales, por lo que es importante investigar cuál es el papel de este factor tanto en la patofisiología de los gliomas malignos, como en otros tumores cerebrales. En este estudio medimos la concentración intratumoral de HGF en neoplasias humanas intracraneales y la correlacionamos con el pronóstico, recurrencia tumoral, edema vasogénico, índice de proliferación celular y densidad vascular.

Métodos

La concentración de HGF se midió en 62 tumores intracraneales, incluyendo 16 astrocitomas anaplásicos (AA), 16 glioblastomas multiformes (GM), 11 meningiomas, 9 adenomas hipofisiarios, 7 oligodendrogliomas, 3 cordomas y 4 muestras de tejido cerebral no neoplásico. Los siguientes parámetros se correlacionaron con los valores de HGF: sobrevida y recurrencia tumoral, índice de proliferación tumoral, densidad vascular (determinada por un análisis inmunohistopatológico) y edema peritumoral (evaluado por estudios de resonancia magnética).

Resultados

La concentración de HGF (pg/mL) fue significativamente mayor en los gliomas malignos (AA y GM) que en los adenomas, oligodendrogliomas y tejido cerebral no neoplásico, pero fue similar a la concentración en meningiomas. La sobrevida media de los pacientes con AA fue de 16.5 ± 3.6 meses y para los pacientes con GM 12.3 ± 1.3 meses. La concentración de HGF fue mayor en GM que en AA (15 844 ± 2504 vs. 7499 ± 1703, $p = 0.0375$), lo que se correlacionó con el índice de proliferación celular y pobre pronóstico. Así mismo, la concentración tumoral media de HGF fue mayor en meningiomas recurrentes que en aquellos sin recurrencia (22 887 ± 6489 vs. 2090 ± 497, $p = 0.008$).

Conclusiones

La concentración intratumoral de HGF en gliomas está asociada con malignidad y pobre pronóstico. Un nivel elevado de HGF también fue encontrado en meningiomas y relacionado con recurrencia a largo plazo. Estos resultados sugieren que la medición rutinaria de HGF podría ser utilizada como factor predictivo dentro de la planeación de estrategias terapéuticas tanto en gliomas malignos como en meningiomas. El uso potencial de inhibidores o antagonistas de HGF para el tratamiento de estas neoplasias debe ser evaluado.

II. INTRODUCCIÓN Y MARCO TEÓRICO

Las neoplasias intracraneales incluyen una gran diversidad de tumores con orígenes histopatológicos, pronósticos y tratamientos diferentes [1]. Los gliomas malignos como el astrocitoma anaplásico (AA) y el glioblastoma multiforme (GM), son los tumores gliales más frecuentes: su incidencia es de 4/100 00 [2], lo que representa el 2% de todos los tumores malignos en adultos. Los gliomas malignos tienen mal pronóstico. La sobrevida media de los pacientes con GM es de un año y esto no se ha modificado significativamente en las últimas tres décadas [3]. Similarmente, la sobrevida de los pacientes con AA es menor a tres años [4-5]. Por lo tanto, es muy importante entender su patofisiología e identificar factores pronósticos. Tanto los GM como los AA tienen índices de proliferación elevados y una intensa vascularidad [6-7]. Estas condiciones están relacionadas con su habilidad para producir factores de crecimiento como el del endotelio vascular (VEGF, de sus siglas en inglés), el derivado de plaquetas (PDGF, de sus siglas en inglés) y el de fibroblastos (FGF, de sus siglas en inglés) [8-18].

Los meningiomas representan aproximadamente el 20% de todas las neoplasias intracraneales, con una incidencia anual cercana al 8 por 100 000 habitantes y por lo general son benignos, por lo que la cirugía es curativa. Sin embargo, sólo el 20% de los meningiomas son reportados como resecados completamente después de una cirugía y más del 80% de los reportados como parcialmente resecados, recurren en los siguientes diez años; por lo que es necesario que después de la segunda cirugía los pacientes reciban radioterapia [19-20].

El factor de crecimiento hepatocítico (HGF, por sus siglas en inglés), también llamado factor de dispersión (scatter factor), es una proteína multifuncional con un fuerte efecto mitogénico sobre los hepatocitos. Inicialmente fue aislado como un péptido relacionado con la regeneración hepatocítica [21-23] y es considerado un indicador de funcionamiento hepático después de la hepatectomía [24-25]. Esta proteína está conformada por una cadena pesada (60kD) de cuatro dominios y una cadena ligera (32kD) y se une a través de su receptor tipo tirosin-cinasa a un producto del proto-oncogen c-Met. El HGF, secretado por células mesenquimales, actúa como un efector parácrino sobre diferentes células epiteliales, induciendo mitogénesis y estimulando la motilidad celular [26-29]. También es un factor angiogénico potente para las células endoteliales *in vitro* e *in vivo* [30]. Se piensa que en hígado y riñón podría ser un factor antiapoptótico [31] y se ha demostrado su necesidad para la embriogénesis como regulador de migración celular y crecimiento. El HGF también es producido por otras células, como los osteoclastos, participando en la regulación de la remodelación ósea y se ha evidenciado que su producción por monocitos juega un papel en la regulación de la hematopoyesis, estimulando el crecimiento y la diferenciación de los precursores eritroides [32].

Los ratones *knock-out* para el gen HGF presentan múltiples anormalidades en el hígado, placenta y sistema nervioso, provocando muerte fetal [33]. Una relación genética entre el HGF y el cáncer ha sido recientemente propuesta ya que se han identificado mutaciones en el dominio catalítico de c-Met en pacientes con carcinoma renal [34]. La sobre-expresión de HGF ha sido determinada en múltiples líneas celulares de leucemia y linfoma [35] y en tumores sólidos de mama [36-38], próstata [39], cólon, hígado [40], riñón [41], cérvix uterino [42], endometrio [43] y vejiga [44]. Además, se ha observado que el HGF promueve la adhesión y la migración de las células cancerosas, debido a la alta afinidad de las integrinas a sus ligandos, un fenómeno relacionado con la tendencia metastásica de los carcinomas [29, 45-46].

Los astrocitos humanos normales expresan HGF y su receptor c-Met [47]. Reportes recientes sugieren que el HGF contribuye a la progresión de gliomas, induciendo angiogénesis y la expresión autócrina adicional de factores angiogénicos como el VEGF [12, 15, 48]. La sobre-expresión de HGF y su receptor c-Met [29] incrementa la motilidad celular y la proliferación de células de glioma humano *in vitro* [50].

El objetivo de este estudio fue relacionar el pronóstico, recurrencia, proliferación celular y la densidad vascular de los gliomas malignos y otros tumores intracraneales con la concentración tumoral de HGF.

Hepatocyte Growth Factor Is Associated with Poor Prognosis of Malignant Gliomas and Is a Predictor for Recurrence of Meningioma

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BACKGROUND. Hepatocyte growth factor (HGF) is a cytokine that participates in multiple cell functions; it promotes proliferation, motility, and morphogenesis of epithelial cells. Some malignant tumors, such as breast carcinoma, bronchogenic carcinoma, and multiple myeloma, overexpress it and its receptor. Hepatocyte growth factor is also present in normal astrocytes; therefore, it is important to investigate whether HGF participates in the pathophysiology of malignant gliomas and other brain tumors. Intratumoral concentration of HGF in human intracranial neoplasms was measured and correlated with prognosis, tumor recurrence, vasogenic edema, cell proliferation index, and vascular density.

METHODS. Hepatocyte growth factor concentration was measured in 62 intracranial tumors, including 16 anaplasic astrocytomas (AA), 16 glioblastoma multiformes (GM), 11 meningiomas, 9 hypophyseal adenomas, 7 oligodendrogliomas, and 3 cordomas, and in 4 samples of nonneoplastic brain tissue. The following parameters were correlated with HGF values: survival and tumor recurrence, cell proliferation index and vascular density as determined by immunohistopathologic analysis, and peritumoral edema as seen by magnetic resonance imaging.

RESULTS. Hepatocyte growth factor concentration (pg/mL) was significantly higher in malignant gliomas (AA and GM) than in adenomas, oligodendrogliomas, and nonneoplastic brain tissue, but it was similar to that of meningiomas. Mean survival of patients with AA was 16.5 ± 3.6 months and for patients with GM 12.3 ± 1.3 months. Hepatocyte growth factor concentration was higher in GM than in AA (15,844 ± 2504 vs. 7499 ± 1703, $P = 0.0375$) and was correlated with the cell proliferation index and with poor prognosis. Likewise, mean tumoral concentration of HGF was higher in meningiomas that relapsed than in those without recurrence (22,887 ± 6489 vs. 2090 ± 497, $P = 0.008$).

CONCLUSIONS. Intratumoral concentration of HGF in gliomas is associated with malignancy and poor prognosis. High HGF is also found in meningiomas and is related with long term recurrence. The current findings suggest that the routine measurement of HGF may be used as a predictive factor for planning therapeutic strategies in both malignant gliomas and meningiomas. The potential use of HGF inhibitors or antagonists for therapy of these tumors should be explored. *Cancer* 2002;94:3210–8. © *2002 American Cancer Society.*
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KEYWORDS: glioblastoma, astrocytoma, angiogenesis, hepatocyte growth factor, brain tumors, meningioma.

Intracranial neoplasms include a great diversity of tumors with different histopathologic origins, prognoses and treatments:[1] Malignant gliomas such as anaplastic astrocytoma (AA) and glioblastoma multiforme (GM) are the most frequent glial tumors: their incidence

is 4/100,000,[2] and they account for 2% of all malignant tumors in adults. Malignant gliomas are still associated with poor prognosis; the mean survival time of patients with GM is one year, and that has not changed significantly for the last three decades.[3] Similarly, the survival for patients with AA is less than three years.[4–5] Therefore, it is of paramount importance to understand their pathophysiology and to identify prognostic factors. Both GM and AA have high proliferation indeces and intense vascularity.[6–7] These conditions are related to their ability to produce growth factors such as endothelial growth factor (VEGF), platelet derived growth factor (PDGF), and fibroblastic growth factor (FGF).[8–18]

Meningiomas account for 20% of all intracranial neoplasms, and their annual incidence is about 8 per 100,000 habitants.[2] They are mostly benign, and surgery is the definitive treatment. However, 20% of meningiomas are reported after surgery as completely resected by surgery, and more than 80% of those that have been partially resected, relapse within the following 10 years. It is customary that after a second surgical resection the patient receive radiotherapy.[19–20]

Hepatocyte growth factor (HGF), also called scatter factor, is a multifunction protein with a strong mitogenic effect on hepatocytes. It was initially isolated as a peptide related to hepatic regeneration.[21–23] It is considered an indicator of hepatic function after hepatectomy.[24–25] This protein is constituted by a heavy chain (60 kD) with four domains and a light chain (32 kD); it binds through its tirosine-kinase receptor, a product of the proto-oncogene c-Met. Hepatocyte growth factor, secreted by mesenchymal cells, acts as a paracrine effector on different epithelial cells inducing mitogenesis and stimulating cellular motility.[26–29] It is also a powerful angiogenic factor for endothelial cells in vitro and in vivo.[30] In the liver and kidney, it may have a role as an antiapoptotic factor.[31] It is also necessary for embriogenesis as a regulator of cell migration and growth. Hepatocyte growth factor is also produced by other cells, such as osteoclasts, participating in the regulation of bone remodeling; its production by monocytes has a role in the regulation of hematopoyesis by stimulation of growth and differentiation of erythroid precursors.[32]

Knock-out mice for the HGF gene have several abnormalities in the liver, placenta, and nervous system causing fetal death.[33] A direct genetic relation between HGF and cancer has also been recently proposed when mutations in the catalytic domain of c-Met from patients with renal carcinoma were identified.[34] Overexpression of HGF has been found in various cells lines of leukemia and lymphoma[35] and in solid tumors of the breast,[36–38] prostate,[39] colon, liver,[40] kidney,[41] uterine cervix,[42] endometrium,[43] and bladder.[44] Hepatocyte growth factor also promotes adhesion and migration of cancer cells, due to the high affinity of integrins to their ligands, a phenomenon related to the metastatic tendency of carcinomas.[29,45–46]

Normal human astrocytes express HGF and its receptor c-Met.[47] Recent findings suggest that HGF contributes to glioma progression, inducing angiogenesis and the expression of additional angiogenic autocrine factors such as VEGF.[12,15,48] The overexpression of HGF and its receptor c-Met[49] increases cell motility and proliferation of human glioma cells in vitro.[50]

The aim of the current study was to relate the prognosis, recurrence, cell proliferation, and vascular density of malignant gliomas and other intracranial tumors with the tumoral concentration of HGF.

PATIENTS AND METHODS

Experimental Design and Patients

This was a prospective study carried out at the Instituto Nacional de Neurología y Neurocirugía de Mexico. Tumoral tissue from 62 patients who underwent surgery from March of 1995 to March of 1998 was studied; 32 patients had malignant gliomas (16 GM and 16 AA), 11 had meningioma, 9 had hypophyseal adenoma, 7 had oligodendroglioma, and 3 had cordoma. Patients who had previously received chemotherapy or radiotherapy were not included. Four samples of nonneoplastic human brain obtained by surgery for epilepsy were used as controls. Tissue was frozen in liquid nitrogen and kept at −70 °C until HGF determination. Patients were followed for a mean of 36 months (range, 3 to 5 years). All patients with malignant glioma were treated under the same scheme, surgery followed by radiotherapy and chemotherapy. Survival time was measured from the date of diagnosis. Patients who had been lost to followup by the time of analysis (March 2001) were contacted by telephone or telegram.

Determination of HGF Concentration

All samples were defrozen, weighted, and homogenized in saline solution with protease inhibitors. The tissue concentration of HGF was determined by enzyme-linked immunosorbent assay Quantikine human HGF immunoassay DHG00; R&D System, Minneapolis, MN) in a 50 μL sample. Assays were made in duplicate and reported as means.

Determination of Vascular Density and Cell Proliferation Index

A small tissue sample was fixed with 10% formalin, and 5 μm width slices were obtained. A hematoxylin and eosin stain was used to make histologic diagnoses.

Additional samples were used for immunohistochemistry with the avidin-biotin-peroxidase complex and counterstained with hematoxylin; they were incubated overnight at 4 °C either with rabbit anti-human factor VIII-related antigen (PCNA; DAKO, Carpinteria, CA) as a marker for vascular endothelial cells or with mouse anti-proliferation cell nuclear antigen (DAKO) as a marker for cellular synthesis phase. A pathologist (D.R.) blind to the results of HGF determination and clinical data counted the number of capillaries positive for factor VIII and the number of cell nuclei positive for nuclear antigen found per microscopic field at × 40 magnification in 10 different fields.

Vasogenic Edema Index

To determine brain edema associated with the tumor as seen by magnetic resonance imaging (MRI), we modified the methods used in previous reports.[16,51] Total tumor area was determined in the axial T1-weighted image. The area of edema was determined in the axial T2-weighted image. The maximal tumor height and the maximal edema height were determined by coronal T1 and T2 weighted images, respectively. These parameters were multiplied (tumor area × tumor height and edema area × edema height) and used as tumor and edema volume, respectively. The relation between both volumes was considered the edema index; when it was above 1 vasogenic edema was considered present.

Tumor Recurrence

Tumor relapse was determined by clinical and imaging evidence of tumor growth after surgery.

Statistical Analysis

Hepatocyte growth factor concentration, vascular density, nuclear cell proliferation index, mitotic index, tumor edema index, and survival time were expressed as means ± standard error. Statistical comparisons between HGF concentrations according to histologic diagnoses were made by the Student *t* test. Statistical differences between HGF concentration and vascular density and mitotic index and cell proliferation index were determined by ANOVA and Turkey tests. Survival (as a dependent variable) was analyzed with the Kolmogorov-Smirnov test to demostrate normal distribution. Correlations between HGF concentration and age, gender, histologic diagnosis, survival, vascular density, cell proliferation, and mitotic index were made by multiple logistic regression analysis. The chi-square test was used to associate the percentage of meningiomas with or without recurrence and HGF concentrations. Statistic significance was determined at $P < 0.05$.

RESULTS

Histopathologic Diagnosis of Intracranial Tumors

From the total of 62 tumors, 25% were AA, 25% GM, 17% meningioma, 14% hypophyseal adenoma, 11% oligodendroglioma, and 5% cordoma, plus 4 control samples of nonneoplastic brain tissue reported as gliosis.

Survival of Patients with Malignant Gliomas

For patients with anaplasic astrocytoma, survival was 16.5 ± 1.2 months. For patients with glioblastoma multiforme, survival was 12.3 ± 1.4 months ($P = 0.09$). Patients with AA and GM showed an inverse relation between HGF concentration and survival ($r = 0.75$ and $P < 0.001$), either as a single group (malignant gliomas) or as individual groups (Table 1 and Fig. 1). All data underwent multivariate analysis, and we found that the association between HGF concentrations and survival was independent of age ($P = 0.979$), gender ($P = 0.543$), and diagnosis ($P = 0.548$).

Hepatocyte Growth Factor Concentration in Neoplastic and Nonneoplastic Tissue

Hepatocyte growth factor levels were higher in GM than in AA (15,844 ± 2504 vs. 7499 ± 1703 pg/mL, $P = 0.0375$). Mean HGF concentration in malignant gliomas (AA plus GM) was 12,393 ± 1645 pg/mL, significantly higher than in hypophyseal adenomas (2088 ± 470 pg/mL, $P < 0.01$), oligodendrogliomas (2966 ± 464 pg/mL, $P < 0.05$), cordomas (3806 ± 1445 pg/mL, $P < 0.05$), and nonneoplastic brain tissue (2658 ± 2379 pg/mL). However, similar to malignant gliomas, meningiomas contained high amounts of HGF (12,486.8 ± 4619 pg/mL, $P = 0.157$).

Histopathologic Analysis

The mitotic index in malignant astrocytomas was 11.1 ± 1.4, vascular density was 53.4 ± 11.5, and the cell proliferation index was 170 ± 41. In meningiomas, the mitotic index was 10.9 ± 3.9, vascular density was 56.8 ± 2.6, and the cell proliferation index was 33 ± 7. In patients with malignant glioma, a significant association was found between HGF levels and the mitotic index ($r = 0.48$ and $P < 0.05$), cell proliferation index ($r = 0.557$ and $P = 0.02$), and tumoral edema ($r = 0.834$ and $P < 0.0001$); vascular density was not significant ($r = 0.56$ and $P = 0.32$) (Fig. 2).

Meningioma Relapse and HGF Concentrations

Table 2 shows the levels of HGF in five patients with completely resected meningiomas that relapsed within the first three years compared with five patients without relapse. Hepatocyte growth factor concentra-

TABLE 1
Intratumoral Concentration of HGF and Survival of Patients with Malignant Glioma

Histology	Age/Gender	HGF (pg/mL)	Survival (months)
Glioblastoma multiforme			
	30/M	31,175	3
	60/F	27,490	9
	60/F	33,980	5
	53/M	27,490	10
	90/M	18,485	7
	68/F	10,261	14
	53/M	15,281	5
	56/M	2828	22
	46/M	18,495	18
	35/M	3019	23
	61/M	10,630	3
	31/M	8128	17
	62/M	5495	26
	54/M	20,265	10
	20/F	20,168	1
	38/M	3210	23
Total	51 ± 17	15,844 ± 2504	12 ± 1
Anaplastic astrocytoma			
	75/F	22,387	2
	74/M	22,119	4
	24/M	19,195	6
	61/F	13,019	8
	42/M	10,642	11
	34/M	10,630	12
	46/F	8550	24
	56/F	6606	12
	58/F	5623	36
	55/F	4365	20
	56/M	3162	27
	62/M	3090	22
	60/F	3019	19
	48/F	2951	18
	56/M	2754	16
	51/F	2042	27
Total	53 ± 13	7499 ± 1703	17 ± 1
Malignant glioma	52 ± 15	12,393 ± 1645	13 ± 1

HGF: hepatocyte growth factor.

tion was significantly higher in meningiomas that later recurred (22,887 ± 6489 pg/mL) than in those without recurrence (2090 ± 497 pg/mL, $P = 0.008$). This association was independent of age ($P = 0.892$) and gender ($P = 0.163$) in a multivariate analysis. In meningiomas with high HGF concentration (> 4000 pg/mL) the percentage of recurrence (chi–square = 6.818, $P = 0.009$), mitotic index, and cell proliferation index were higher ($P < 0.01$) as compared to meningiomas with lower HGF concentration (< 4000 pg/mL).

DISCUSSION

Tumoral concentration of HGF in malignant gliomas and in meningiomas is greatly increased in comparison with other intracranial tumors and with nontumoral brain tissue. We found that HGF is a strong independent prognostic marker in malignant gliomas; it is also related to cell proliferation and to peritumoral edema, supporting previous reports that emphasize its importance in the pathogenesis of these tumors. In addition, we found that HGF is expressed in a variable way in meningiomas, and that its expression is related with the cell proliferation index and with its ability to relapse.

Hepatocyte growth factor and its receptor (c-Met) have been detected in normal astrocytes, in human gliomas, and in other malignant tumors.[12,50,52–53] In human cultured glioma cells, HGF and c-Met are simultaneously expressed, with an autocrinous effect inducing cell proliferation and migration.[50]

A common cause of failure of treatment of malignant gliomas is resistance to radiotherapy and chemotherapy; the mechanism by which the cell survives these treatments involves the production of growth factors that regulate DNA repair and apoptosis. In vitro and in vivo, HGF inhibits drug-induced cytotoxicity and apoptosis in experimental neoplasms treated by radiation, cisplatin, and camptothencin;[54] this effect might decrease the therapeutic response of patients with high intratumoral levels of HGF. There is intense infiltration by microglia in gliomas, which may enhance malignancy by secretion of epidermoid growth factor and by inhibition of cytotoxic lymphocytes;[55] in vitro studies have shown that HGF stimulates the microglial infiltration of gliomas, favoring their growth.[56]

The direct correlation of cell proliferation (as evidenced by increase of PCNA) with the presence of HGF supports its participation in tumoral growth of glioma, as has been shown for other tumors such as breast carcinoma.[57]

The mechanism by which HGF stimulates cell proliferation seems to be related to the tirosine kinase activity of its receptor, which involves Ras and mitosis activation proteins.[58–59] Such effects could be antagonized by tirosine kinase inhibitors. However, not all HGF effects require phosphorylation of its receptor; for instance, its antiapoptotic effect is independent, suggesting that it could also participate in the genesis of the tumor. The insertion of the HGF gene in human glioma cells increases proliferation of independent colonies in vitro and tumorigenesis in vivo.[49]

There are some histologic features of malignant glioma associated with prognosis, such as the extent of necrosis or vascular density.[60] Hepatocyte growth factor is a strong inductor of angiogenesis; its effects are synergistic with other growth factors such as VEGF and bFGF. However, in the current study, we did not

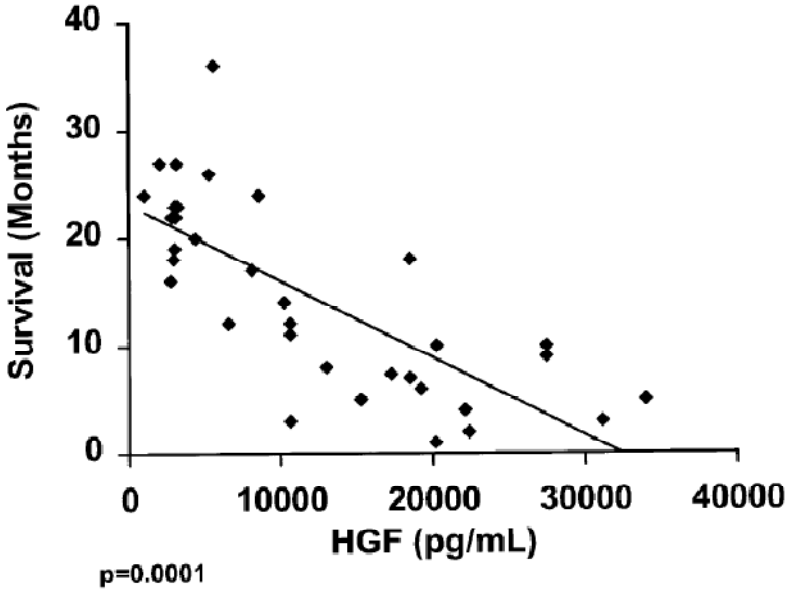

FIGURE 1. Individual correlation between survival of patients with malignant glioma (anaplastic astrocytomas and glioblastoma multiforme) and intratumoral concentration of hepatocyte growth factor (HGF) ($P < 0.01$).

TABLE 2
Intratumoral Concentration of HGF in Meningiomas with and without Recurrence

	Recurrence			No recurrence	
Meningioma	Age/Gender	HGF (pg/mL)		Age/Gender	HGF (pg/mL)
	50/F	40,365		66/M	1564
	60/F	15,840		62/F	812
	58/M	4365		65/F	1445
	42/M	19,887		29/F	2630
	38/F	33,980		55/F	3981
Total	50 ± 9	22,887 ± 6489	Total	55 ± 15	2090 ± 497

HGF: hepatocyte growth factor.

find a clear relation between vascular density and HGF concentration. This could be due to the fact that only patients with high grade gliomas (GM and AA) were included; in these cases, neovascularization with spontaneous vascular occlusions are common, and large areas of necrosis are a consequence. This possibility could be better explored in low grade gliomas, which were not included in the current study. The progression to malignancy in gliomas could be associated with high concentrations of various growth factors, leading to increased vascular density[48] and breakage of the hematoencephalic barrier, which would induce cerebral edema, a complication associated with increased morbidity.

We found a direct relation between peritumoral edema and HGF contents, independent of vascular density. Previous studies have shown that HGF increases the permeability of the hematoencephalic barrier, independently of VEGF expression, possibly by the induction of endothelial fenestrations and by the tumoral expression of proteases such as urokinase and extracellular matrix metaloproteins.[61]

According to the current results, HGF could represent not only a prognostic factor for survival, but also an attractive target for new therapeutic schemes because its inhibition could produce antiangiogenic and antiprolifferative effects, enhancing the responses to chemotherapy and radiotherapy. An experimental approach is the transference of the HGF/NK2 gene to human glioma cells; this natural blocker of HGF ac-

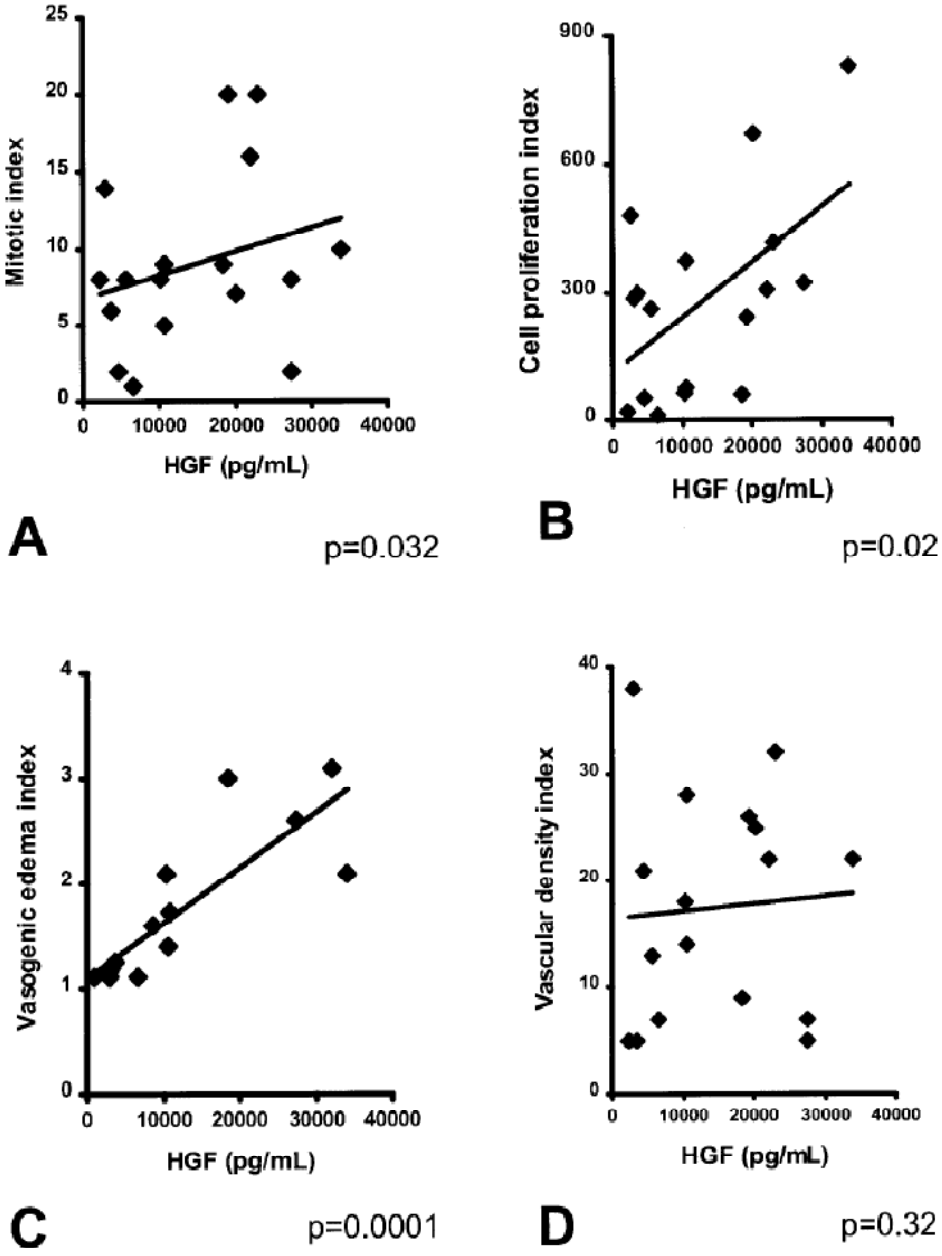

FIGURE 2. Individual correlations between intratumoral concentration of hepatocyte growth factor (HGF) and A) mitotic index, B) cell proliferation index, C) vasogenic edema index, and D) vascular density index.

tivity decreases tumor activity and overexpression of HGF.[62]

We also found, high concentration of HGF in meningiomas, at levels similar to those found in malignant gliomas, but with great individual variations. Previous studies have shown a co-expression of c-Met and HGF in 85% of meningiomas[13] and, lack of relation between HGF and tumoral angiogenesis.[63] As for malignant gliomas, we found a correlation between HGF concentration and cell proliferation markers in meningioma, indicating that it could be used as a predictor for recurrence, a circumstance that currently is difficult to anticipate but is present in 15 to 20% of patients with meningioma. Few factors can be used as predictors for relapse; among them are VEGF concentration, cellular atypia, and markers of cell proliferation.[64–66] If corroborated in a large number of patients, the current findings could support the use of HGF as a predictor for relapse in order to implement additional therapeutic measures, like the early administration of radiotherapy and/or chemotherapy in patients whose tumors had high HGF concentrations.[67]

As both groups of neoplasms are easily distinguished from each other on histologic and clinical grounds, the current findings could have various implications for research and for practical grounds. In the case of malignant gliomas, HGF measurement could be used as a predictive element directly related with the degree of malignancy and could help to determine the need for aggressive therapy. In addition, therapeutic attempts could be made to block HGF receptors as a potential adjuvant treatment. In the case of meningiomas, as neither histopathologic nor clinical data are currently taken as reliable recurrence predictors, HGF could be used as a reliable element for predicting tumor recurrence after surgical extirpation.

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II. CONCLUSIONES

Los gliomas malignos como los meningiomas se distinguen fácilmente a partir de sus características clínicas e histológicas, los datos publicados en este estudio podrían tener varias implicaciones para investigaciones futuras y para la práctica clínica. En el caso de los gliomas malignos, la medida de HGF podría ser utilizada como elemento predictivo directamente relacionado con el grado de malignidad, ayudando a determinar la necesidad de tratamientos más agresivos. Además, se pueden desarrollar abordajes terapéuticos dirigidos al bloqueo de los receptores de HGF. En el caso de los meningiomas, actualmente los datos clínicos o histopatológicos no son considerados como predictores fiables de recurrencia, por lo que los niveles de HGF podrían ser utilizados como un elemento fiable para la predicción de recurrencia tumoral después de la resección quirúrgica.

En resumen, la concentración intratumoral de HGF en gliomas se asocia con malignidad y pobre pronóstico. Concentraciones elevadas de HGF también fueron demostradas en meningiomas y se asociaron con recurrencia a largo plazo. Estas observaciones, sugieren que la determinación rutinaria de HGF podría ser utilizada como factor predictivo para la planeación de estrategias terapéuticas tanto en gliomas malignos como en meningiomas. El uso potencial de inhibidores o antagonistas de HGF para el tratamiento de estos tumores debe ser evaluado.

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