Cavernous Sinus Invasion and Tumor Proliferative Potential of Growth Hormone-Producing Pituitary Tumors

TOSHIHIKO IUCHI, NAOKATSU SAEKI, YOSHIO UCHINO, YOSHINORI HIGUCHI, ICHIRO TATSUNO*, SUSUMU NAKAMURA*, TOSHIYUKI YASUDA** AND AKIRA YAMAURA

Department of Neurological Surgery, Chiba University School of Medicine, 1–8–1 Inohana, Chuo-ku, Chiba 260–8670, Japan

** 2nd Department of Internal Medicine, Chiba University School of Medicine, 1–8–1 Inohana, Chuo-ku, Chiba 260–8670, Japan*

*** Department of Pediatrics, Chiba University School of Medicine, 1–8–1 Inohana, Chuo-ku, Chiba 260–8670, Japan*

Abstract. *Purpose* Surgical removal of growth hormone-producing pituitary adenomas (GHomas) becomes difficult when they invade the cavernous sinus (CS). We investigated the relation among tumor proliferative potential, tumor volume and invasion of GHomas to CS. *Materials & Methods* 15 patients with GHoma aged 20–59 years were enrolled. The volumes of the adenomas were calculated from MR images and the extension to CS was classified into 5 grades according to Knosp's grading system. The immuno-histochemical staining for anti-Ki-67 monoclonal antibody (MIB-1) was performed and the proliferative potential of GHomas was determined as the percentage of MIB-1 labeled nuclei (MIB-1 index). The volume, MIB-1 index and pre-operative growth hormone (GH) level were compared with CS invasion by single and multiple regression analyses. *Results* With single regression analyses, CS invasion was significantly correlated with both the volume ($r=0.69$, $p<0.01$) and MIB-1 index ($r=0.73$, $p<0.01$), but not with the GH level ($r=0.42$, $p=0.12$). The volume and MIB-1 index showed a weak correlation but it was not significant ($r=0.52$, $p=0.06$). With multiple regression analysis, CS invasion was well explained by the volume and MIB-1 index of GHomas ($r=0.82$, $p<0.01$). About 66% of CS invasion was explained by these two factors. *Conclusions* In view of these results, not only the volume but also the speed of growth are important for GHomas to invade CS. GHomas with a high MIB-1 index may, even if they are small, more readily invade CS and need closer post-operative hormonal and neuroimaging studies.

Key words: Pituitary adenoma, Growth hormone, Cavernous sinus, Ki-67

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THE growth hormone-producing pituitary adenomas (GHomas) are generally histologically benign tumors, but surgical treatment becomes difficult when they invade the cavernous sinus (CS). Although the mechanism of invasion is not certain, the tumor proliferative potential, mechanical compression and chemical proteolysis may be candidates. The purpose of this study is to investigate the relation among tumor proliferative potential, tumor volume and the extent of CS invasion of GHomas.

Materials and Methods

Fifteen patients with GHoma aged 20–59 years were enrolled. They were 9 men and 6 women. The volume of the adenomas was calculated from MR images and the extension to CS was classified into 5 grades according to Knosp's grading system [1] as follows: Grade 0, adenomas with no CS invasion; Grade 1, adenomas not pass the intercarotid line; Grade 2, adenomas pass the intercarotid line but not extending beyond the lateral aspects of the internal carotid arteries (ICAs); Grade 3, adenomas pass the lateral aspects of the ICAs but do not encase the ICAs; Grade 4, adenomas with total encasement of the intracavernous ICAs.

Correspondence to: Toshihiko IUCHI M.D., Department of Neurological Surgery, Chiba University School of Medicine 1–8–1 Inohana, Chuo-ku, Chiba 260–8670, Japan

Table 1. Clinical and pathological characteristics of 15 GH-producing pituitary tumors

Case No.	Age (yrs)	Knosp's grade of Cavernous Sinus Invasion	serum GH (ng/ml)	volume (cm ³)	MIB-1 index (%)
1	20	0	15	0.36	1.25
2	45	0	12	1.13	0.16
3	59	1	35	2.18	0.46
4	48	1	16	0.55	0.57
5	48	1	43	0.76	1.08
6	54	1	64	3.00	0.75
7	36	2	110	4.40	0.82
8	53	2	439	15.36	n.d.*
9	36	2	44	1.98	0.83
10	45	2	33	7.56	0.56
11	49	3	15	0.93	1.19
12	43	3	21	12.81	1.84
13	54	3	18	10.50	1.40
14	47	4	140	49.80	1.52
15	27	4	411	17.64	1.93

*n.d. not determined

Four micro-meter thick sections from formalin fixed, paraffin embedded specimens were heated in an autoclave for 20 minutes at 120°C in 10 mM citrate buffer (pH 6.0) and stained immunohistochemically with anti-Ki-67 monoclonal antibody (MIB-1, dilution 1:40, Immunoteck, Marseille, France). The proliferative potential of GHomas was determined as the percentage of MIB-1 labeled nuclei (MIB-1 index) [2].

The volume, MIB-1 index and pre-operative growth hormone (GH) level were compared with CS invasion by single and multiple regression analyses.

Results

The mean volume of all adenomas was $8.58 \pm 12.72 \text{ ml}$ (mean $\pm$ S.D.). The volume of highly invasive tumors (Grades 3 and 4, $18.28 \pm 18.48 \text{ ml}$, mean $\pm$ S.D.) was significantly larger than that of less invasive tumors (Grade 0, 1, and 2, $3.73 \pm 4.64 \text{ ml}$, $p < 0.05$), but there was no significant difference between highly and less invasive adenomas in the serum GH level ($p = 0.62$).

The mean value for the MIB-1 index of 15 GHomas was $1.03 \pm 0.53\%$ (mean $\pm$ S.D.). The MIB-1 index of Grades 3 and 4 ($1.58 \pm 0.09\%$, mean $\pm$ S.D.)

Fig. 1. Graphs showing the relationship between volume (a), MIB-1 index (b), or serum GH before surgery (c) and the extent of cavernous sinus invasion.

was significantly higher than that of Grade 0, 1 and 2 (0.72 ± 0.11 , $p < 0.001$).

With single regression analyses, the extent of CS invasion was significantly correlated with both the volume ($r = 0.69$, $p < 0.01$, Fig. 1-a) and MIB-1 index ($r = 0.73$, $p < 0.01$, Fig. 1-b), but not with the serum GH level ($r = 0.42$, $p = 0.12$, Fig. 1-c). The volume and MIB-1 index showed a weak correlation but it was not significant ($r = 0.52$, $p = 0.06$). With multiple regression analysis, CS invasion was well explained by the volume and MIB-1 index of GHomas ($r = 0.82$, $p < 0.01$). About 66% of CS invasion was explained by these two factors.

Discussion

The treatment of large GHomas with CS invasion is very difficult. The existence and the extent of invasion to the CS is one of the most important factors for success in surgical treatment of these tumors. Magnetic resonance imaging realized the visualiza-

tion of CS invasion [3–6], and we can evaluate the extent of invasion before surgery.

From our results, the volume and the speed of growth are two independent important factors related to CS invasion of GHomas. In our series, all adenomas which extended beyond the lateral aspects of ICAs (Grade 3 and 4) showed more than 1.00% MIB-1 indices. When we take a look at an individual case, however, Case 11 had an adenoma with a 1.19% MIB-1 index with CS invasion (Grade 3) even though the volume was only 0.93 ml. This case shows that GHomas with a high MIB-1 index may, even if they are small, more readily invade the CS and need closer post-operative hormonal and neuroimaging studies. But since not all cases of CS invasion were attributable to these two factors alone, the presence of another factor such as chemical proteolysis has been suggested [7].

We concluded that the volume and proliferative potential play important roles in CS invasion by GHomas.

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