Relationship Between the Proliferative Ability of Meningiomas and the Recurrence After the Tumor Total Removal (attaching 136 case reports)

Tao Xin[1], Xiaoqing Yang[1], Xu Zhao[2], Jianjun Wang[3], Liangzhu Teng[1*]

1. Department of neurosurgery, Shandong Provincial Hospital, Jinan, 250000, China
2. Department of neurosurgery, The Second Affiliated Hospital of Shan Dong University, jinan 250000 China
3. Department of neurosurgery, Shan Dong Qian fo Shan Hospital, Jinan 250000, china

Abstract **Objective** To understand the relationship between the proliferative activity of meningiomas and the recurrence after the meningiomas total removal. **Methods** The data of the disease course, the pathological changes of 16 patients with the recurrent meningioma and 120 patients with non-recurrent tumor were analyzed, the tumor specimen were tested by flow cytometry (FCM) in 60 patients among them. **Results** The recurrent group was with a shorter course of disease than that of the non recurrent one, the recurrent meningiomas had higher scores in loss of architecture, hypercellurarity, nuclear pleomorphism, mitotic rate, focal necrosis than the non-recurrent group; in the order of the rate, the recurrence were decreased as the anaplasitc, the atypical and the benign meningiomas, the recurrent group had higher hyperdipoid tumor, and higher DNA index (DI) and proliferative index (PI) compared with the non-recurrent one. **Conclusions** The proliferative ability of the tumor was close related with the recurrence after meningioma total resection. The active proliferation of the tumor was one of the important factors of the recurrence after the meningioma total removal.

Key Words Meningioma; Recurrence; Proliferative

Meningioma is the most common intracranial benign tumor and is mainly cured by surgical removal. But there are still some recurrences after the surgical removal. According to Marimanoff [1] statistic, the recurrence of 5 years、10 years、15 years is 7%、20% and 32% after the total removaland is 37%、 55% and 91% after subtotal removal respectively. Besides the extent of the removal, the proliferative ability of meningiomas has a great impact on the recurrence of the meningiomas. So, we randomly draw off the data of the 136 patients (Simpson Ⅰ~Ⅱ) that we accept and give a total surgical removal, and have a retrospective pathologic analysis. 60 cases are done by flow cytometry (FCM) to explore the relationship between the proliferative ability of meningiomas and the recurrence of the dise.

*correspondence to: Liangzhu Teng
E–Mail: tenglz@126.com
TEL: 0531–51862352)

MATERIALS AND METHODS

General data 136 patients with meningiomas who had been undergone the total surgical removal operations in shandong provicial hospital were collected in this experiment, they were followed up 5 to 10 years (average 7.35 years), and were divided into recurrent group and non-recurrent group basing on the result of the following up. The non-recurrent group is 120 cases, male 39 cases, female 81 cases, the ages of them ranged from 17~67, averaging 45.48 years old; the recurrent group is 16 cases, male 9 cases, female 7 cases, aging from 25~63, averaging 39.88 years old.

The tumor location 45 cases on convexity of brain, 21 cases near sagittal sinus, 26 cases on cerebral falx, 12 cases on sphenoidal crest, 4 cases in lateral cerebral ventricle, 3 cases in olfactory groove, 4 cases on tuberculum sellae, 3 cases in middle cranial fossa, 18 cases in back cranial fossa. All the cases are given the total removal (Simpson Ⅰ~Ⅱ).

Pathohistologic changes According to the

pathologic subtype of WHO standard [2] and Mahmood [3] method, counting histologic scores on the base of the six pathologic indexes (loss of architecture、 hypercellurarity、 nuclear pleomorphism、 mitotic rate、 focal necrosis and brain infiltration), the former five indexes calculate 0~3 scores accordingly, and brain infiltration calculates 0~2 scores. According to the sum of the score, divide the tumor into benign (Ⅰ degree, 0~4 scores)、 atypism (Ⅱ degree, 5~11 scores) and anaplasia form (Ⅲ degree, >11 scores).

FCM analysis Take the fresh tumor tissue about 5 mm in diameter on operation from 60 patients (48 non recurrence, 12 recurrence), frozen by liquid nitrogen, analyzed them in batch. Prepare the cell suspension by nest twisting method, dyed with Propidium iodide, tested by FACScan flow cytometry equipment (Becton-Dickson company), put the normal lymph cell as the interior reference, coefficient variation(CV) 2.25%~4.50%, and detect 1000 cells in each sample. The equipment records the result automatically. DNA index(DI) is calculated as follows:

$$DI=\frac{\text{the average GO/G1 from the sample}}{\text{the average GO/G1 of the normal lymph cell in the same batch}}$$

Put the 1±CV as diploid, DI = 1.0±0.1 is diploid, DI<0.9 is subdiploid, DI>1.1 is hyperdiploid. Nondiploid is called heteroploid.

②proliferation index(PI) is calculated as follows:

$$PI=\frac{S+G2/M}{G0/G1+S+G2/M}$$

RESULT

Gender and age Male: female in non-recurrent group=1: 2.07, and in recurrent group =1: 0.78, there are more males in the later group, but there is no significant difference between the two groups (P>0.05). There is also no significant difference in age between the two groups (P>0.05).

Disease course The disease course before the surgery in this data ranged from 0.4~360 months. The middle disease course is 13 months in non-recurrent group, and is 3 months in the recurrent group, the difference between them is significant in statistics (P<0.01, Mann-Whitney test).

Pathologic detection ①pathologic hypotype: the sum of each pathological type in all the 16 recurrent cases is as follow: zoarium type 9 cases (9/42, 21.4%), fibrous type 4 cases (4/57, 7.0%), mixed type 2 cases (2/32, 6.3%), vascular matricyte type 1 cases(1/5), the recurrent rate of the zoarium type obviously higher than that of the fibrous type (P<0.005). ②The comparison of the two groups histologic scores is illustrated by table 1. ③pathologic degree: the recurrent rates of benign, atypical and anaplasia form are 3.6% (3/82)、 15.9%(7/44) and 60.0% (6/10) respectively, statistical analysis shows that the rate of anaplasia form obviously higher than that of the other two groups (P<0.025~0.005), and the rate of atypical form is higher than that of benign form (p<0.005.) ④FCM analyze: a. DNA polidy: among the 48 cases of the non-recurrent group, diploid tumor 26 cases, hyperdiploid tumor 13 cases, hypodiloid tumor 9 cases; among the 12 cases in the recurrent group, diploid tumor 5 cases, hyperdiploid tumor 7 cases. The rate of hyperdiploid and heterodiploid in the recurrent group is obviously higher than that in the non-recurrent group (p<0.05). b. comparison of the DI and PI: DI in the recurrent group is 1.12±0.08, noticeable higher than that in the non-recurrent group (1.01±0.11) (P<0.05); PI in the recurrent group (28.13±8.69)% is also noticeable higher than that in the non-recurrent group (17.09±7.52)% (P<0.05).

Table 1 comparison of the two groups histologic scores ($\bar{X}$±S)

Group	n	Loss of architecture	hypercellurarity	nuclear pleomorphism	mitotic rate	focal necrosis	brain infiltration
Recurrence	16	2.01±0.86*	2.06±0.89*	1.52±0.68*	0.77±0.82*	0.82±0.75*	0.48±0.83△
Non-recurrence	120	1.09±0.80	1.19±0.56	1.16±0.60	0.10±0.31	0.12±0.42	0.26±0.61

* Compared to the non-recurrent group P<0.01; △P<0.05.

DISCUSSION

The results of this experiment show that the proliferative ability is the most important factor for the recurrence after the meningiomas total removal. The tumor with active proliferation grows fast, and the volume increases obviously in short-term, and which inclined to form encephaledema around the tumor[4]. These factors can cause the clinic symptom incur and aggravate in short-term, which make the patient diagnosed early, so the disease course is short. The six indexes (loss of architecture、hypercellurarity、nuclear pleomorphism、mitotic rate、focal necrosis、brain infiltration) are used to asses benign or malignant degree by WHO. The result shows that except the index of the brain infiltration the other five indexes make significant difference. Monte [5] studied the 22 histologic characteristics, found that seven indexes (mitotic rate、focal necrosis、loss of architecture、increase of blood vessel ingredient、conspicuous nucleoli、hypercellurarity and hemosiderin pigmentation) are relevant with the recurrence. The three indexes (loss of architecture、less than 10% of the meningeal endothelial cell and conspicuous nucleoli) have significant relationship with the short recurrent interval, meantime the recurrent interval of tumor with two or three indexes is obviously shorter than the one of tumor with only one index. There is major dispute about which pathologic characteristic is most meaningful to the tumor´ recurrence at present. Perry[6] considers that mitotic rate is an important index, the possibility of the recurrent tumor with 4 mitoschisis phrases per high eyesight (4M F/HPF) increases, higher than the one with 20MF/HPF. Mclean[7] considers focal necrosis as an important index for prediction of the tumor´ recurrence, but Younis [8] regards that the brain infiltration is more important than the focal necrosis in the recurrence of the tumor. This result shows that brain infiltration makes no difference in the two groups. Maybe the location of the histologic tissues is different, and the index of brain infiltration is unreliable if the tissues are taken from the central tumor.

This data shows that the pathologic classification is closely related with the meningeoma recurrence after the removal. The recurrence rates of the Simpson Ⅰ-Ⅲ degree are 3.16%、15.19%、60% respectively, which is similar to the result of the Jaaskelainen[9] who studies that the recurrence of the tumor with Simpson Ⅰ-Ⅲ degree are 3%, 38% and 78%, and the recurrent rate increases with the degree of the histologic classify.

It is partial to predict the meningiomas recurrent rate simply by the pathologic characteristic, because the recurrence is not only limited in the meningiomas with the malignant characteristics, but aslo sometimes the meningiomas with the benign characteristic will recur and even metastasis. Pathologic determination of meningioma is easily subjectively influenced by the pathologist. The different pathologists will make a different determination on the same sample. So the biological behavior of meningiomas should not only be determined by the pathologic characteristic, but also including other factors. FCM is a new method of studying the tumor biological behavior. It can analyze generous cell、the DNA content in the tumor、distribution of each cell cycle、the cell apoptosis and so on. In this data, the hyperdiploid rate、DI and PI in the recurrent group is obviously higher than the one in the non-recurrent group. FCM not only reflects the ploidy and the content of the DNA, but also the S period cell and PI. The increase of the PI and DI means the proliferation of tumor actively, and inclined to recur. May[10] finds that PI of meningioma in the recurrent group is higher than that in the non-recurrent group, so he considers PI as an important index for the prognosis of the meningioma.

The recurrence of the meningioma has close relationship with the poliferative ability of the meningioma, which is the most important factor for the prognosis of meningioma except the extent of the removal. Determination of the tumor after the removal should base on the clinic, pathology and the index of reflecting the proliferative ability (FCM、PCNA). As to the meningioma with active proliferation, radiotherapy (external irradiation, X-knife, γ-knife) should be given after the removal in order to postpone and avoid of the recurrence of the tumor.

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