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BRAIN TUMOR AND CEREBRAL CIRCULATION

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In the daily clinical practice it is of utmost importance to evaluate the state of cerebral circulation of the patient. Many investigators, therefore, have worked on the subject of cerebral circulation, though rather little progress has been made because of morphological specificity of the cerebral blood vessels, complicity of cerebrovascular anastomoses, great difference between man and experimental animal and great experimental difficulty due to vital and delicate nature of the brain tissue.

The applied experimental approaches to the study of cerebral circulation may be classified into direct and indirect methods. The direct method is those of following three ways. The first is skull window method originated by Forbes(1) in 1928 in which changes of the pial vessels are observed through an artificial window of the skull with the aid of binocular microscopes. This method is not suitable for man except in special occasions, but it is capable for animal experiments. Shortcomings of this method lie in that it does not give the overall picture of the cerebral circulation because we can neither determine the absolute volume of cerebral blood flow in a cirtain time by this method nor we can assume that pial vessels and vessels deeper in the brain substance yield indentical response to a same stimulus. The second method is by way of observation of the blood vessels of the ocular fundi which was introduced by Gollwitzer-Meier et al(2) in 1932. In Japan we have excellent reports by Uemura(3) in 1953. Clinically the cerebral blood vessels are closely related with ophthalmic and central retinal arteries, and the observation of blood vessels of the fundi yields information concerning cerebral circulation. This method is easily applicable on man. It has the same advantage and disadvantage with the skull window method. We are only guessing the cerebral blood flow through observation of the blood vessels of the ocular fundi until we materialize simultaneous determination of cerebral and retinal blood flows. The last of the direct methods is perfusion technique performed by Dixon and Halliburton(4) in 1910, Brown(5) in 1916, Handley(6) in 1943 and Geiger and Magnes(7) in 1947. Disadvantages of this method are firstly there are more than a single blood vessel flowing into the brain contrary to elsewhere of the body, secondly operation is complicated and last it is done under unphysiological conditions. The main virtue of this method is that it can eliminate several variable factors pertaining to general body functions. It is, however, not applicable on man.

For the indirect method there are about five different technical devices. The first is by means of flow meter. In this category there are orifice meter by Gregg(8) in 1940, rotatometer by Gregg et al(9) in 1942, bubble meter by Schmidt(10) in 1943, thermostromuhr by Rein(11) in 1934, electromagnetic flow meter by Kolin(12) in 1936, needle thermoelectric blood flow recorder by Gibbs(13) in 1933 and so forth. The thermocouple of Gibbs may be placed either in the blood vessel or in the tissue. Merits of this method are that it is operated under nearly physiological conditions, it is applicable on human subject when inserted into cerebral veins and it permits detection of changes within a localized area of the brain. The method has disadvantages in that it is not specific for indicating changes in blood flow since the temperature as indicator of this method may also vary with changes in other variables than blood flow and it requires insertion of the thermocouple causing unavoidable trauma to the tissue. If those factors are eliminated as much as possible and appropriate controls taken, this is a simple and excellent method for study of changes in cerebral blood flow. Next is by determination of the liquor pressure or liquor volume and there are two methods. One is a method to know the state of cerebral blood flow by quantitating the fluctuation of cerebrospinal fluid pressure. Harada et al(14) in 1937 showed that increase and decrease of the cerebral blood flow paralleled to those of the liquor pressure. Zeisho (15) in 1951 compared this method with the thermo-electric method and disclosed that though increase and decrease of the cerebral blood flow caused ascent and descent of the liquor pressure, slight fluctuation of the liquor pressure did not cause changes in the blood flow. The other was devised by Ferris(16), who determined absolute volume of blood collecting in the brain by measuring volume of liquor displaced from the subarachnoid space through a lumbar puncture needle when a special cuff around the subject's neck was inflated to 80 mm H_2O to halt outflow of the internal jugular vein for several minutes. These methods can be applied on human subjects and it enables us to know the increase and decrease of cerebral blood flow, though the absolute volume can not be obtained by this method. The third is dye dilution method by Gibbs. It is based on Stewart[17] principle that the dye injected into an artery is diluted while passing through an organ and blood flow of the organ is measured by the dye dilution. As for the brain dilution of dye injected into the internal carotid artery is determined by its concentration in the internal jugular vein. This method requires only a short time. Demerits of this method lie in that there are numerous inflow and outflow for the cerebral circulation and that dye injected into the internal carotid artery on one side is not diluted evenly throughout the whole brain but shows up in much higher concentration in the internal jugular vein on the same side than on the other side, necessitating adoption of the mean value of both concentrations. The fourth is of gas analysis of blood. It was devised by Weis and Lennox[18] in 1931 who determined cerebral blood flow by means of speed of cerebral circulation indicated by changes in values of oxygen and carbon dioxide in the blood. Cerebral arteriovenous oxygen difference is a product of correlation between cerebral blood flow and cerebral oxygen consumption, and it does not yield a separate value of either of them by itself. Kety and Schmidt[19] in 1945 originated nitrous oxide method. This indicates cerebral blood flow by determination of nitrous oxide concentrations in arterial and cerebral venous blood after inhalation of nitrous oxide. This is widely approved by many authors as a most reliable method for clinical use. Since the introduction of the nitrous oxide method there have been many brilliant works published in various parts of the world. In Japan Aizawa et al[20] presented a report by nitrous oxide method in 1952 and many others have followed since. The nitrous oxide procedure requires ten minutes for operation and skill for collecting blood samples. It is not suitable for anemic patients, for required amount of blood samples is a lot. Its standard deviation is inevitably great due to complicated anatomy of cerebral blood vessels. Despite these shortcomings nitrous oxide method is regarded by many investigators to be most valid and reliable when compared with other previous methods. After the original method of Kety and Schmidt there came out modifications of Sheinberg and Stead[21] in 1948 and of Aizawa[22] in 1953.

As for the subject of cerebral circulation in cases of brain tumor, reports have been scanty. Kety et al[23], Bernsmeier and Siemons[24] and Aizawa et al[22,25,26] made some reports on this subject. We want to present interesting results obtained in our clinical study of cerebral circulation in cases of brain tumor.

METHOD OF RESEARCH

Twenty two cases of brain tumors who visited the Surgical Department of the Keio University Hospital were subjected to the study of cerebral circulation by means of the original method of Kety and Schmidt. The patient inhaled the nitrous oxide mixture consisting of 15% N_2O, 21% O_2 and 64% N_2 through a mask with one-way stopcocks. As is shown in the figure 1, blood samples were collected simultaneously from femoral artery and internal jugular vein just

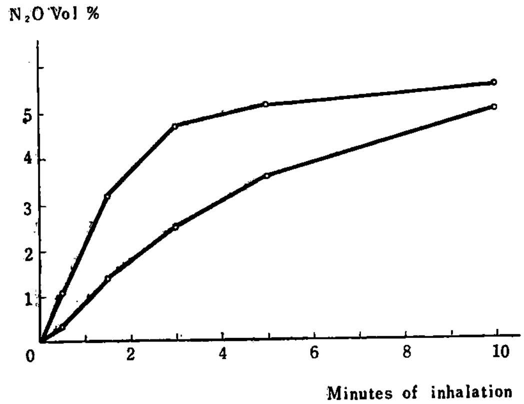

Fig. 1 Time (indicated by ○) of collecting blood samples in N_2O procedure after original method of Kety & Schmidt.

before the beginning of inhalation for the first sample and afterwards exactly 30 seconds, 1 minute and 30 seconds, 3 minutes, 5 minutes and 10 minutes after inhalation. Procaine was infiltrated locally over respective spots for placing the needle which were prepared beforehand by filling the dead space with heparin solution. Blood samples were drawn simultaneously from femoral artery and internal jugular vein at times designated above and were analyzed for gas consumption by means of Macro Van Slyke-Neill manometric apparatus. The cerebral blood flow was then formulated according to Fick principle and calculated by means of trapezoid rule. Cerebral oxygen consumption was calculated from cerebral arteriovenous oxygen difference and cerebral blood flow. Mean arterial blood pressure was derived as sum of the diastolic blood pressure measured by Riva Rocci manometer and one third of the pulse pressure. Cerebrovascular resistance was calculated from mean arterial blood pressure and cerebral blood flow.

The technical terms, formula of calculation and units of cerebral circulation are listed below.

Cerebral blood flow:

$$CBF = \frac{100V_{10}}{\int_0^{10}(A-V)dt} \quad (cc/100\,g\ brain/min)$$

Cerebral arteriovenous oxygen difference:

$$(A-V)O_2 \ (vol.\,\%)$$

Cerebral oxygen consumption:

$$CMRO_2 = \frac{(A-V)O_2 \times CBF}{100} \quad (cc/100\,g\ brain/min)$$

Mean arterial blood pressure:

$$MABP = \text{Mean Femoral Arterial Pressure}$$
$$\doteqdot \text{Diastolic Pressure} + \frac{\text{Pulse Pressure}}{3} \quad (mm\,Hg)$$

Cerebrovascular resistance:

$$CVR \doteqdot \frac{MABP}{CBF} \quad (mm\,Hg/cc\ blood/100\,g\ brain/min)$$

RESULTS OF RESEARCH

The cerebral circulation was measured on 22 patients with brain tumor who presented themselves to the Surgical Department of the Keio University Hospital. The results of measurement are shown in the table 1.

Table 1
Tabulation of Data

Patient No.	CBF	$CMRO_2$	CVR	MABP	$(A\text{-}V)O_2$	L. D.
1	40.7	1.1	2.4	98	2.8	300
2	39.4	2.3	2.4	93	5.8	330
3	32.9	1.8	2.4	78	5.5	450
4	45.1	2.2	1.6	74	4.9	180
5	39.8	1.5	1.9	83	3.8	330
6	42.9	2.2	2.2	93	6.6	250
7	45.2	2.8	1.8	81	6.3	120
8	41.8	2.6	2.2	92	6.2	170
9	35.5	1.9	2.8	100	5.4	470
10	41.3	2.1	2.5	103	5.0	480
11	46.7	1.4	2.1	99	3.1	55
12	37.5	2.3	2.8	104	6.1	250
13	34.4	1.9	2.0	70	4.3	400
14	42.6	1.8	1.9	93	4.3	110
15	43.0	2.8	1.9	80	6.0	250
16	44.5	2.5	2.2	98	4.1	370

17	48.2	2.6	2.1	103	5.3	180
18	30.7	1.5	3.2	103	5.0	230
19	45.8	2.2	1.9	89	4.9	330
20	42.8	2.3	1.9	81	5.3	270
21	40.0	2.2	2.3	90	5.4	480
22	53.8	3.0	1.9	105	5.5	
Average:	41.6	2.2	2.2			
Normal Value (Kety & Schmidt)	54*	3.3**	1.6***			

* cc/100 g brain/min. ** cc/100 g brain/min. *** mm Hg/cc blood/100 g brain/min.

Generally speaking there are decrease of cerebral blood flow, decrease of cerebral oxygen consumption and increase of cerebrovascular resistance. The cerebral

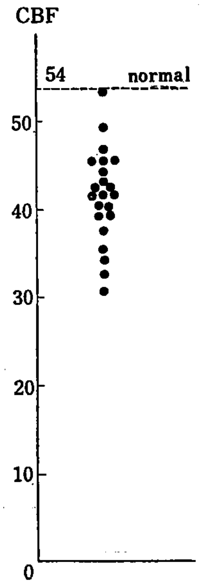

Fig. 2

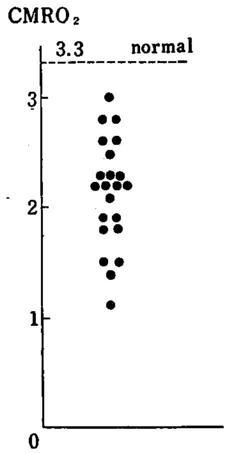

Fig. 3

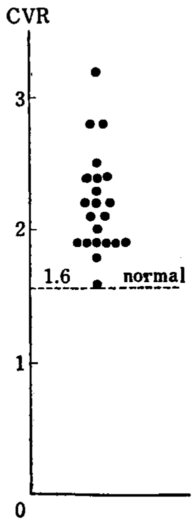

Fig. 4

Each dot is plotting of a case.

blood flow is depicted on the figure 2, the cerebral oxygen consumption on the figure 3 and cerebrovascular resistance on the figure 4. They show the aforementioned tendency clearly.

The table 2 shows data of cerebral circulation from the standpoint of location of the brain tumor whether it is supra- or infra-tentorial. There is no obvious difference in values of cerebral circulation between supra- and infratentorial tumors, though the latter seems to show higher degree of decrease in cerebral blood flow. In supratentorial tumors average cerebral blood flow is 42.8, average cerebral oxygen consumption 2.2 and average cerebrovascular

Table 2

Location of Brain Tumor and Cerebral Circulation

	Location	Patient No.	CBF	$CMRO_2$	CVR	MABP	L. D.
SUPRATENTORIAL	Parietal	1	40.7	1.1	2.4	98	300
		7	45.2	2.8	1.8	81	120
	Frontal	6	42.9	2.2	2.2	93	250
	Temporal	5	30.7	1.5	3.2	103	230
		22	53.8	3.0	1.9	105	
	Base (including pituitary)	2	39.4	2.3	2.4	93	330
		4	45.1	2.2	1.6	74	180
		8	41.8	2.6	2.2	72	170
INFRATENTORIAL	Cerebellum	10	41.3	2.1	2.5	103	480
		13	34.4	1.9	2.0	70	400
		20	42.8	2.3	1.9	81	270
		15	43.0	2.8	1.9	80	250
	Base (including acoustic neurinoma)	16	44.5	2.5	2.2	98	370
		11	46.7	1.4	2.1	99	55
		12	37.5	2.3	2.8	104	250
		21	40.0	2.2	2.3	90	480
		9	35.5	1.9	2.8	100	470

resistance 2.2, while in infratentorial tumors average cerebral blood flow 40.6, average cerebral oxygen consumption 2.2 and average cerebrovascular resistance 2.3.

From the standpoint of pathological varieties of brain tumor, no obvious correlation is seen betwen sorts of brain tumor and changes in various values of cerebral circulation as is shown in table 3.

Several cases will be introduced followingly. Case No. 13 in the group of neuroglioma was a case of cerebellar neuroglioma complicated with obstructive hydrocephalus and an advanced intracranial pressure elevation with liquor pressure of 400 mm H_2O. Results of measurement in this case were markedly decreased cerebral blood flow of 34.4, similarly decreased cerebral oxygen consumption of 1.9 and slightly increased cerebrovascular resistance of 2.0. Case No. 1 had a giant meningioma widely involving temporo-parietal region, whose cerebral blood flow was 40.7 of moderate decrease, cerebral oxygen consumption 1.1 of marked decrease and cerebrovascular resistance 2.4 of moderate increase in degree. Case No. 10 among the group of hemangioma had a hemangioma located in the posterior cranial fossa. There was an excessive intracranial pressure elevation with liquor pressure of 480 mm H_2O and advanced obstructive hydrocephalus, but decrease of cerebral blood flow was unexpectedly low, that is 41.3. Cerebral oxygen consumption decreased moderately and cerebrovascular

Table 3
Kinds of Brain Tumor and Cerebral Circulation

Kinds of tumor	Patient No.	CBF	$CMRO_2$	CVR	MABP	L. D.
Neuroglioma	6	42.9	2.2	2.2	93	250
	7	45.2	2.8	1.8	81	120
	2	39.4	2.3	2.4	93	330
	13	39.4	1.9	2.0	70	400
	15	43.0	2.8	1.9	80	250
	20	42.8	2.3	1.9	81	270
Meningioma	1	40.7	1.1	2.4	98	300
Hemangioma	10	41.3	2.1	2.5	103	480
	4	45.1	2.2	1.6	74	180
Pituitary tumors	8	41.8	2.6	2.2	92	170
Acoustic neurinoma	21	40.0	2.2	2.3	90	480
Cysts	18	30.7	1.5	3.2	103	230
Cholesteatoma	22	53.8	3.0	1.9	105	
Adhesive arachnoiditis	5	39.8	1.5	1.9	83	330
	16	44.5	2.5	2.2	98	370
	11	46.7	1.4	2.1	99	55
	12	37.5	2.3	2.8	104	250
	9	35.5	1.9	2.8	100	470

Table 4
Comparison of Values Before (b) and after (a) Surgery

Patient No.	Tumor	Surgery	Time	CBF	$CMRO_2$	CVR
16	Cerebellar tumor	Torkildsen operation	b.	47.3	2.1	2.1
			a.	50.5	2.4	1.9
10	Cerebellar hemangioma	Torkildsen operation	b.	41.3	2.1	2.5
			a.	50.9	3.0	1.7
1	Parietal meningioma	Removal of tumor	b.	40.7	1.1	2.4
			a.	45.2	1.9	2.2
2	Neuroglioma of the base	Partial removal of tumor	b.	39.4	2.3	2.4
			a.	32.5	1.6	3.5
12	Tumor of the posterior cranial fossa	Torkildsen operation	b.	37.5	2.3	2.8
			a.	43.8	2.8	2.3
9	Cerebellar tumor	Torkildsen operation	b.	35.5	1.9	2.8
			a.	44.5	2.5	2.2
6	Neuroglioma of the anterior cranial fossa	Removal of tumor	b.	42.9	2.2	2.2
			a.	48.3	3.2	1.9
7	Parietal neuroglioma	Removal of tumor	b.	45.2	2.8	1.8
			a.	49.6	3.0	1.6

18	Cyst of cerebrum	Removal of cyst	b.	30.7	1.5	3.2
			a.	50.7	2.8	2.5
21	Tumor of the cerebello-pontile angle	Removal and Torkildsen	b.	40.0	2.2	2.3
			a.	48.3	2.6	2.0

resistance increased moderately. Case No. 18 was a case of giant cyst in the left temporal lobe whose cerebral blood flow showed prominent decrease of 30.7. Cerebral oxygen consumption also showed quite a decrease, and cerebrovascular resistance prominent increase. In case No. 9 who had arachnitis complicated with excessive intracranial pressure elevation with liquor pressure of 470 mm H_2O, there were marked decrease of cerebral blood flow, marked decrease of cerebral oxygen consumption and moderate increase of cerebrovascular resistance.

In ten cases out of this series various values of cerebral circulation were measured before and after surgery of brain tumor. As for the surgical procedures five cases had removal of brain tumor, four had Torkildsen operation which was for ventricular shunt by means of a tube passing from a lateral ventricle to the cisterna magna and one had combination of both procedures. Results of those ten cases are listed on the table 4 which discloses postoperative improvement in form of increase of cerebral blood flow, increase of cerebral oxygen consumption and decrease of cerebrovascular resistance in all cases except

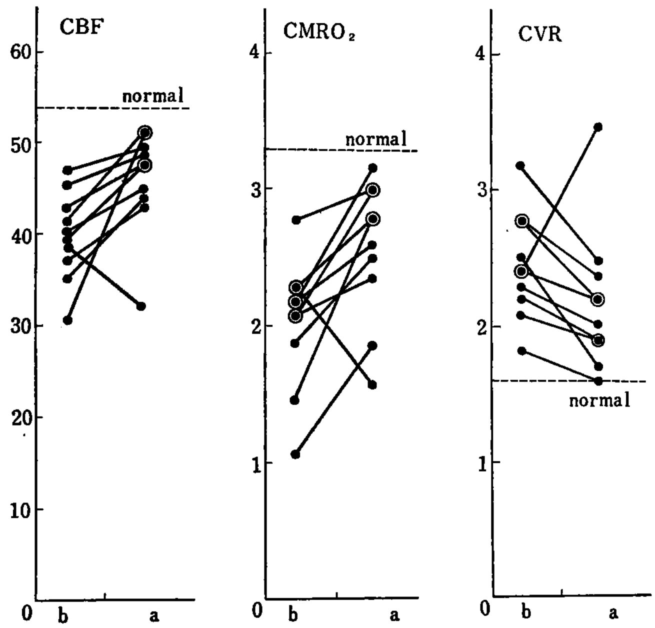

Fig. 5 Comparison before (b) and after (a) surgery.

case No. 2. Preoperative and postoperative measurements of cerebral circulation are depicted on the figure 5, which clearly demonstrates benefit of surgery. Case No. 2, a single exception, had an extensive neuroglioma originating in the base of skull. At surgery only a part of the tumor was removed and naturally no postoperative improvement in various values of cerebral circulation was expected.

The figure 6 illustrates relationship between degree of elevation of intracranial pressure and cerebral blood flow. Generally speaking there is a decrease of cerebral blood flow in cases of brain tumor and there is precipitous fall of cerebral blood flow as the liquor pressure becomes higher than 350 mm H_2O.

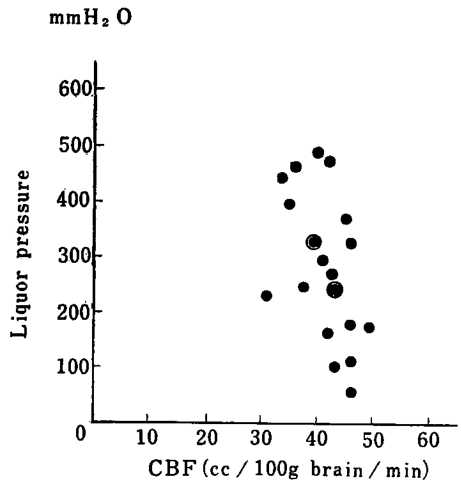

Fig. 6 Liquor pressure and CBF.

DISCUSSION

Since Kety and Schmidt released nitrous oxide method in 1945 as a procedure for clinical and experimental observation of cerebral circulation, there have been many brilliant accomplishments in various parts of the world. Works on cerebral circulation, however, in cases of brain tumor by means of nitrous oxide method have been scanty so far and it is referred only to reports by Kety and Schmidt, Bernsmeier and Siemons, Aizawa and Yoshino et al.

When a space occupying process such as brain tumor occurs in the cranium, the cerebral blood flow is ruled by Munro-Kellie-Cushing(27) doctrine that when there is a increase of intracranial pressure there are associated increase of cerebrovascular resistance and decrease of cerebral blood flow. This has been advocated for considerably long time.

Kety measured cerebral circulation on 13 cases of brain tumor by means of nitrous oxide method and found correlation between liquor pressure and cerebral blood flow that when liquor pressure became elevated the cerebrovascular resistance increased and cerebral blood flow decreased unless there was compensatory mechanism. He says decrease of cerebral blood flow, until the liquor pressure reaches level of 450 mm H_2O, induces progressive cerebral asphyxia which stimulates vasomotor center and raises arterial pressure compensatorily in order to overcome the increased vascular resistance, and 450 mm H_2O is estimated as threshold of liquor pressure elevation to cause disturbance of cerebral circulation. Bernsmeier et al performed measurements of cerebral circulation by means of nitrous oxide method on 22 cases of elevated intracranial pressure including cases of brain tumor and found that in cases of prominent intracranial pressure elevation there was significant decrease of cerebral blood flow which paralled clinical symptoms. According to the report of Aizawa et al. on 2 cases of brain tumor there were prominent decrease of cerebral blood flow, decrease of cerebral oxygen consumption and increase of cerebrovascular resistance, though liquor pressure was lower than the threshold value of Kety. In the report of Yoshino(28) on 3 cases of brain tumor with elevated liquor pressure above 420 mm H_2O, there were prominent decrease of cerebral blood flow and cerebral oxygen consumption and prominent increase of cerebrovascular resistance in all cases.

Results of our study showed decrease of cerebral blood flow, decrease of cerebral oxygen consumption and increase of cerebrovascular resistance in almost all cases of brain tumor. The decrease of cerebral blood flow tends to be greater in degree as elevation of liquor pressure grows higher and there is only slight decrease of cerebral blood flow in general as long as liquor pressure is below 350 mm H_2O. We, therefore, consider 350 mm H_2O to be the threshold. This coincides with the results of Ferris(16) who used plethysmograph for measurement of cerebral circulation and stated 350 mm H_2O to be the threshold.

As for location of brain tumor Kety described that there was prominent decrease of cerebral blood flow especially in tumors of posterior cranial fossa and decrease was not so prominent in the supratentorial tumors. In our cases there were similar tendency but it was not so remarkable as was described by Kety.

From the standpoint of kinds of brain tumor and as for hemangioma in the first place Shenkin et al(29) reported that due to arteriovenous shunt in cerebral hemangioma there were increase of cerebral blood flow, decrease of cerebrovascular resistance and normal cerebral oxygen consumption. We studied two cases of hemangioma. Case No. 10 was a rare case of cavernous hemangioma located in the posterior cranial fossa and blocked circulation of cerebrospinal fluid causing hydrocephalus with marked elevation of intracranial pressure. In this case as was confirmed by surgery and vertebral angiography there was coexistence of decreased cerebral blood flow due to elevated intracranial pressure on one hand and increased cerebral blood flow due to hemangioma on the other hand, and in the net result there were slight decrease of cerebral blood flow, slight decrease of cerebral oxygen consumption and increase of cerebrovascular resistance. Case No. 4 had a small hemangioma located in the anterior cranial fossa and showed only trivial deviation in various values of cerebral circulation. As for meningioma case No. 1 in table 1 had a huge meningioma located extensively over temporo-parietal region which measured 100 g when removed by surgery. The liquor pressure in this case was 300 mm H_2O and the cerebral blood flow was 40.7. The decrease of cerebral blood flow is not as marked as it would be expected from the huge size of the tumor. This we consider is because the tumor had a supratentorial location which caused only mild elevation of liquor pressure and because the tumor itself had good blood supply due to abundant vascularity by nature of meningioma. By the way Bernsmeier et al reported a case of meningioma with prominent increase of cerebral blood flow instead of decrease.

It is, though as it might be expected, extremely interesting and important that pathological changes in various values of cerebral circulation in case of brain tumor were ameliorated remarkably by either surgical removal of the tumor or Torkildsen operation in which flow of liquor is shunt from the lateral venticle to the cisterna magna for decrease of liquor pressure.

We made experiments on dogs in order to study cerebral circulation in simulated brain tumor with elevated intracranial pressure by means of inflation of a balloon placed in the epidural space up to 300, 500 and 700 mm H_2O, and results of measurements of various values of cerebral circulation were reported[30]. It was noticed that the higher the degree of inflation of the balloon the more prominent was the decrease of cerebral blood flow. Results of animal experiments for elevated intracranial pressure and brain tumor with such an acute production of elevated liquor pressure and simulated brain tumor as by means of inflation of epidural balloon are not as valid as clinical cases of brain tumor with chronic course. We consider decrease of cerebral blood flow in the experimental animal was caused by increased cerebrovascular resistance due to liquor pressure elevation and compression of cerebral vessels by inflated balloon. Yoshino performed animal experiments of intracranial pressure elevation with measurement of cerebral circulation by means of injecting sodium chloride solution into the cisterna magna. There was a dog in which liquor pressure of 300 mm H_2O already caused some influence upon cerebral circulation, and in all dogs there was disturbance of cerebral circulation when liquor pressure was elevated higher than 400 mm H_2O. The cerebral blood flow, therefore, seems to decrease whenever there is a brain tumor associated with intracranial pressure elevation even before the liquor pressure reaches hight of 400 mm H_2O.

CONCLUSION

1. Clinical studies were performed to investigate the influence of brain tumor upon cerebral circulation by means of nitrous oxide method.

2. The cerebral circulation was measured on 22 cases of brain tumor who visited the Surgical Department of the Keio University Hospital. In general patients with brain tumor had decreased cerebral blood flow, decreased cerebral oxygen consumption and increased cerebrovascular resistance.

3. Improvement was noticed in changes in various values of cerebral circulation when intracranial pressure was decreased either by surgical removal of the tumor or by Torkildsen operation.

4. The cerebral blood flow decreases when intracranial pressure becomes elevated and we estimate the threshold value of liquor pressure for decrease of cerebral blood flow to be some-place around 350 mm H_2O.

We conclude this report with words of deep gratitude to Dr. Wasaburo Maeda, Proffessor of Surgery, and Dr. Toyozo Aizawa, Professor of Internal Medicine, Keio University, who gave us guide and advice in the study.

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