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Thrombosis and Intracranial Tumors

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Summary. 334 necropsy reports of intracranial neoplasm from an autopsy material over 13 years were reviewed to study the relationship of intracranial tumors to vascular thrombosis. The incidence of venous thrombosis in intracranial tumors was found to be 27.5% while that of a control group without malignancies taken at random from the autopsy material was 17%. The difference gives a statistical significance of $P \leqq 0.05$. The parameters of sex, surgical intervention, the malignancy and the histological type of the tumor apparently do not affect thrombus formation to a statistically significant degree. There is increased thrombosis frequency with increasing age. The presence of hemiparesis or hemiparalysis does not affect the incidence of thrombosis. However, it determines to a great degree the lateralization of the thrombus.

Key words: Venous thrombosis — Intracranial neoplasm — Paraneoplastic syndrome.

Zusammenfassung. Aus den Sektionsprotokollen, die einen Zeitraum von 13 Jahren umfaßten, wurden insgesamt 334 Fälle mit Hirntumoren herausgesucht, um die Beziehung zwischen intrakraniellen Tumoren und vasculären Thrombosen zu untersuchen. Die Koincidenz von venösen Thrombosen und intrakraniellen Tumoren ergibt sich zu 27,5%, die Thrombosehäufigkeit in einer zufällig ausgewählten Kontrollgruppe ohne Tumoren jedoch nur zu 17%. Der Unterschied ist statistisch signifikant auf dem $P \leqq 0{,}05$-Niveau. Eine statistische Signifikanz hinsichtlich verschiedener Faktoren wie Geschlecht, Operation, Malignität und histologischer Typ des Tumors ist nicht gegeben. Die Thrombosehäufigkeit steigt mit zunehmendem Alter an. Die Existenz von Hemiparesen oder Hemiparalysen beeinflußt nicht die Thrombosefrequenz, jedoch bestimmen sie in starkem Maß die Lokalisation der Thrombose.

Introduction

The occurrence of thrombo-embolic phenomena in malignant tumors of epithelial origin is well known. Trousseau (1865) who wrote the first report on this relationship emphasized the development of thrombosis in peripheral veins as one of the early signs of malignant tumor. He himself developed an idiopathic thrombophlebitis which he attributed to an occult neoplasm. Eight months later he died of carcinoma of the stomach. Numerous studies on this subject have been reported since then (Edwards, 1949; Fish *et al.*, 1951; Fisher *et al.*, 1951; Gore, 1953; Henderson, 1955; Kenney, 1943; Korst and Kratchovil, 1955; Lafler and Hinerman, 1961; Osler and McCrae, 1900; Perlow and Daniels, 1956; Sproul, 1938; Thies, 1964). The papers reported the coincidence of thrombus formation mostly with intraabdominal malignancies like carcinoma of the pancreas, stomach,

gall bladder, liver, kidney, urinary bladder, uterus and the ovaries. Thromboembolic phenomena have also been associated with bronchogenic carcinoma as well as carcinoma of the breast, the trachea, the thyroid, the tongue and the skin. Rohner *et al.* (1966) found non-bacterial thrombotic endocarditis and thromboemboli in 16 patients with mucinoid carcinoma. The association of thrombosis with mucin-producing cancers has also been noted by Jennings and Russel (1948), McKay and Wahle (1955), Rosen and Armstrong (1973). Multiple thrombosis and hemorrhagic diathesis have been often observed in carcinoma of the prostate (Tagnon *et al.*, 1953; Prout *et al.*, 1956; Kellock and Gallagher, 1958; Rapaport *et al.*, 1959). Paraneoplastic hemorrhages have also been reported in carcinoma of various other organs (Frick, 1956; Welborn *et al.*, 1964; Bleyl *et al.*, 1971; Warter *et al.*, 1972). Although numerous studies on coagulation disorders in malignancy have been published, to our knowledge there has been, to date, neither a clinical description nor a statistical investigation on this relationship in brain tumors. Recently, we had a young patient with a fibrillary astrocytoma who suddenly developed a deep vein thrombosis in one leg although she was not bedridden and had no hemiparesis; neither did she have any signs of any internal disorder. Another patient had a spongioblastoma, who died within a few days with signs of increased intracranial pressure; autopsy revealed multiple thrombi in the sigmoid and transverse sinuses. Such individual cases are, of course, of no significant value in establishing definite relationships. We found the question interesting enough to be worth following up in a large necropsy material from the Pathological Institute of the University of Heidelberg. The purpose of this investigation was to ascertain the incidence of brain tumors showing thromboembolic phenomena at necropsy, to determine if thrombus formation is related to the degree of malignancy or to the type of the brain growth, to determine if the parameters age, sex, surgical operation and presence of hemiparesis or hemiphlegia play any significant role in thrombus formation in intracranial neoplasms.

Statistical Data

Our statistical results are based on the review of 334 necropsy reports of brain malignancy obtained from 14262 cases in the period from 1960 to 1972. Intracranial metastases from extracranial malignancies were not included in the study. Only macrothrombosis was considered because in a necropsy material it is not always possible to differentiate the micro-thrombi die to intravital intravascular coagulation in the capillaries from the micro-thrombi resulting from postmortem fibrinolysis (Bull and Brain, 1968).

Since there is a greater danger of thrombo-embolic complications after operations, we divided our material into the post-surgical and the non-post-surgical cases. We designated as post-surgical those patients who underwent operation during their last admission to the hospital and died within 4 weeks after operation (the majority of them died within 2 weeks). We grouped as non-post-surgical 2 patients who died 6 weeks after operation, 1 patient 7 weeks and 1 patient 8 weeks after operation, all 4 of which did not have any thrombosis. Also included in the non-post-surgical group were those patients who were never operated on and those who were readmitted because of relapse after a first (or a second)

Table 1. Incidence of thrombosis in post-surgical and non-post-surgical cases

	Number of cases	Cases with thrombosis	Cases with non-limb-thrombosis
Post-surgical	206	56 (27.2%)	17 (8.2%)
Non-post-surgical	128	36 (27.8%)	9 (7%)
Total	334	92 (27.5%)	26 (7.8%)

Table 2

Localisation of the thrombi	Number of cases
Femoral and popliteal v.	76 (74.5%)
Prostate plexus (or ovarian)	11 (10.8%)
V. cava and jugular v.	6 (5.9%)
Cerebral sinuses	6 (5.9%)
Mesenteric v.	1 (1.0%)
Cerebral art.	2 (1.9%)

Table 3. Distribution of intracranial tumors according to histological type, sex and thrombosis

Histological type	Without thrombosis		With thrombosis		Total
	male	female	male	female	
Glioblastoma	39	38	18	16	111
Astrocytoma	25	19	9	5	58
Meningeoma	14	24	7	10	55
Spongioblastoma	13	7	1	3	24
Oligodendroglioma	6	9	3	6	24
Ependymoma	2	10	4	3	19
Medulloblastoma	9	5	0	0	14
Pituitary adenoma	6	1	3	1	11
Neurinoma	3	6	0	0	9
Pinealoma	1	0	2	0	3
Hemangioma	1	2	0	0	3
Angioblastoma	2	0	0	0	2
Plexus papilloma	2	0	0	0	2
Melanoblastoma	1	0	0	0	1
Teratoma	1	0	0	0	1
Margaritoma	0	0	1	0	1
Chordoma	1	0	0	0	1

operation some years or months before the last admission and were not operated on again during their last stay in the hospital.

In our material (334 cases), thrombosis was found in 92 cases (27.5%). 206 cases were post-surgical while 128 cases were non-post-surgical. As shown in Table 1, from the 206 post-surgical cases, 56 cases had a thrombosis (27.2%). In the non-post-surgical group, 36 cases showed thrombosis (27.8%). There is no real difference between the two groups. The localisation of the thrombi is seen in Table 2.

Table 4. Age distribution

Range (years)	Total	Cases with thrombosis	Cases with non-limb-thrombosis
0— 9	38	1 (3%)	0 (0%)
10—19	5	0 (0%)	0 (0%)
20—29	26	8 (30%)	3 (11.5%)
30—39	33	7 (21%)	3 (9.1%)
40—49	55	16 (28%)	6 (11%)
50—59	90	21 (23%)	5 (5.6%)
60—69	66	30 (45%)	8 (12.1%)
70—79	19	8 (42%)	1 (5.3%)
80—99	2	1 (50%)	0 (0%)

Table 5. Frequency of thrombosis and histological type of malignancy disregarding the cases younger than 20 years old

Histological type	Total	With thrombosis
Glioblastoma	106	34 (32%)
Astrocytoma	55	14 (25%)
Meningeoma	54	16 (30%)
Oligodendroglioma	24	9 (38%)
Ependymoma	13	7 (55%)
Spongioblastoma	11	4 (36%)
Pituitary adenoma	11	4 (36%)
Neurinoma	8	0 (0%)
Pinealoma	3	2 (66%)
Medulloblastoma	2	0 (0%)
Margaritoma	1	1 (100%)

The presence of multiple thrombi in some cases explains the discrepancy between the sum of the thrombi and the total number of cases. The most frequent localisation was the veins of the legs, followed by the prostate and ovarian plexus. Eight cases had thrombi in intracranial vessels; 5 of them showed also a limb-vein thrombosis aside from the intracranial thrombosis (3 cerebral sinus thrombi and 2 cerebral artery thrombi). Among the 76 cases with leg vein thromboses pulmonary artery embolism occurred in 71 cases (93%).

The occurrence of thrombosis according to the histological type of tumor and to sex is shown in Table 3. Since 5 cases had two brain tumors of different histological types, the sum of the total tumors differs from the total number of cases. These 5 cases showed the following tumor combination: meningeoma—pituitary adenoma; meningeoma—neurinoma; glioblastoma—pituitary adenoma; glioblastoma—neurinoma; medulloblastoma—spongioblastoma. None had thrombosis. It is noted that the malignancy of the growth had no apparent influence on the incidence of the thrombosis. For instance, the meningeomas show the same incidence of thrombosis as the glioblastomas. In the medulloblastomas and the neurinomas, no thrombosis was found. The age distribution of all tumor cases

Table 6. Incidence of thrombosis in patients with paresis or paralysis

	Without paresis	With paresis	Increased deep reflexes	With paralysis	No data given
Cases with leg vein thrombosis	36 47.5%	26 34%	5 7%	7 9%	2 2.5%
Cases without thrombosis	126 52%	75 31%	18 7.4%	20 8.2%	3 1.2%
Cases without thrombosis, 20 years of age and older	98 49%	71 35.5%	18 9%	13 6.5%	0 0%

Table 7. Distribution of the leg vein thromboses

Localisation of thrombosis	Cases with paresis	Cases with paralysis	Total
Paretic—paralytic leg	15 (58%)	4 (57%)	19 (58%)
Both legs	8 (31%)	3 (43%)	11 (33%)
Contralateral leg	3 (11%)	0 (0%)	3 (9%)

with and without thrombosis can be seen in Table 4. The distribution of the non-limb thromboses is also shown in this table. There was one stillborn with a glioma. The oldest patient was a 94-year-old man with a meningeoma. The age group 60—94 years had the highest incidence of thrombosis.

Table 6 shows the distribution of the cases according to the presence of hemiparesis and hemiparalysis. It is interesting to note that 43% of the cases with limb thrombosis had hemiparesis or hemiparalysis while 54.5% had no weakness of the limbs or had merely an increased activity of the deep tendon reflexes of one side. Among the cases without thrombosis, 59.4% were not paretic or had only an accentuation of the deep reflexes on one side while 39.2% were hemiparetic or hemiparalytic. If we consider only the cases above 20 years of age in this group without thrombosis, 42% was paretic or paralytic while 58% was not. It is noted that the presence of hemiparesis or hemiparalysis does not affect the rate of occurrence of thrombosis. However, in Table 7 it can be seen that the majority of the limb thromboses occur in the paretic or paralytic leg.

Our control group which corresponds to our intracranial tumor material in age and sex distribution comprises 100 necropsy cases without any malignancy taken at random from the autopsy material of the Heidelberg Pathologic Institute. These were cases who had stayed at least 3 weeks in the hospital before death. Cases of sudden death, for example, due to accidents or to myocardial infarction, were not included in the control group.

Discussion

The coincidence of intracranial tumors and thrombosis in our material is 27.5%. The incidence of thrombosis in our control group of 100 necropsy cases without malignancy is 17%. The difference is statistically significant ($P \leqq 0.05$). Conceding

that the presence of a space-occupying mass could alter the hemodynamics within the skull and assuming that this could increase the liability of the blood to clot in the intracranial vessels, the 3 cases with intracranial thrombosis (the other 5 cases with intracranial thrombosis also had limb vein thrombosis) would have to be eliminated. With the resulting 26.9% incidence of thrombosis in our intracranial tumor material we still obtain a statistically significant difference from the control group at the $P \leqq 0.05$ level.

The incidence of thrombosis in intraabdominal malignancy (carcinoma of the stomach, pancreas) is higher, ranging between 45 and 60% with slight variations among the reports in the literature. The explanation for this could be 1. a stronger influence on blood clotting exercised by these tumors, and/or 2. the age distribution of these tumors show a peak in the age group 60—70 years, i.e. 10 years older than the peak in the age distribution of our intracranial tumor material. Table 4 shows that incidence of thrombosis in the age group 60—69 years of our material is 45%.

In our material 93% of the 76 cases with leg vein thrombosis had pulmonary artery embolism. This finding seems to find explanation in a report (Keil, 1957) which describes the paraneoplastic thrombus as loose and non-adherent to the blood vessel wall and, hence, more likely to give off emboli.

The analysis of our material revealed that sex, surgical interference and malignancy do not affect thrombus formation, at least as far as the statistical findings are concerned. Our results show that the incidence of thrombosis in intracranial tumors increases with age (Table 4). Whereas in the age group 1 to 19 years, only one out of a total of 43 cases developed a thrombosis, the incidence increased in the age group 20—59 years to 20—30%, and in the group older than 59 years to 42—50%. This finding is in accordance with the commonly known observation of increased tendency to thrombosis with increasing age in the general population.

If we eliminate our cases younger than 20 years of age, the resulting incidence of thrombosis for every histological type of tumor constitutes 25 to 38% with the exception of the ependymomas (55%) and the pinealomas (66%). However, the number of cases of pinealomas is too limited to be of any significance.

The presence of hemiparesis or hemiparalysis does not affect the incidence of limb vein thrombosis but it does play a role in the localization of the thrombus. If venous thrombosis occurs, it affects in the majority of cases the paretic or paralytic leg or both legs. Using the ^{125}I-labeled fibrinogen technique in a study of patients with cerebrovascular accident, Warlow *et al.* (1972) found that 60% had developed deep vein thrombosis in the paralyzed leg and 7% in the non-paralyzed leg. There is no question that the lack of movement and the blood stasis in the paretic leg favor thrombus formation in that limb. But our data show that hemiparesis alone is not the decisive factor in the development of thrombosis in brain tumor patients.

Previous reports have discussed the possible causative factors and the mechanism of thrombosis as a paraneoplastic syndrome (Sproul, 1938; Thies, 1964; McKay, 1965; Miller *et al.*, 1967; Encke and Saggau, 1971; Amundsen *et al.*, 1967). The consensus of opinion is that there is a hypercoagulability which is due to the release of thromboplastin or thromboplastin-like substances from the tumor tissue. Other authors have reported an increase in platelet aggregation and adhesion with

or without thrombocytosis (Morrison, 1932; Moolten *et al.*, 1949; Savitsky and Werman, 1954; Levin and Conley, 1964; Miller *et al.*, 1967). Fumarola *et al.* (1958) found a shortened recalcification time and elevation of factors II, V and VII. Miller *et al.* (1967) found an increased level of clotting factors and their inhibitors in patients with cancer and proposed that the balance between the two opposing effects is more precarious and appears to be disturbed more easily. Minor disturbances which might be insignificant in normal persons like local infection, tissue trauma or vascular stasis would then be sufficient to set up a chain of reactions in the cancer patient leading to thrombosis and hemorrhage. The mechanism by which the same disturbance may result in two opposite effects is the "defibrination syndrome". However, in most cases the opposing forces cancel each other and there is no clinically manifest thrombosis or hemorrhage.

From the results of our study it is not possible to offer a new explanation for the paraneoplastic thrombus formation. In our investigation we find that the occurrence of venous thrombosis in intracranial neoplasms is significantly increased, that the degree of malignancy and histological type of growth, the sex of the patient, surgical operation and the presence of hemiparesis do not influence the incidence of thrombus formation, and that factors which come along with age do play a role in this relationship. It would seem fair to conclude that the presence of an intracranial tumor alters one or more factors in the complex network in the clotting mechanism.

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