THE LONGEVITY OF PATIENTS WITH GLIOMA GYRIFORME MULTIFORME

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The almost uniformly short life span of patients with glioblastoma multiforme is well known. Many neurosurgeons have based their handling of such patients on this fact. It is therefore of interest when patients with long survival are found. In a review of gliomas at Montefiore Hospital, a few cases were encountered in which the duration was so long that they were deemed worthy of being placed on record. Stimulated by this finding, we have attempted an analysis of factors in prognosis.

MATERIAL

The total number of gliomas reviewed was 165. Of these, 83 (50.4 per cent) were glioblastoma multiforme. For purposes of this presentation, 70 cases were considered. The remainder were omitted mainly because the follow-up was inadequate. Within the group of 70, there were 59 patients who came to necropsy, and 11 in whom the diagnosis was proved by biopsy alone. There were 57 patients upon whom operation was performed, many of these later coming to necropsy. Of these 57 patients, 35 received radiotherapy in addition, and 2 received courses of nitrogen mustard. Of the patients who were not operated upon, only 1 was irradiated.

There was a marked difference in incidence between the sexes; 45 of the patients were males, and 25 females, a ratio of 1.8:1. The age of onset reached its peak in the 6th decade. The youngest patient was 19, the oldest 70. In terms of location of the neoplasm, all patients had some cerebral involvement, but in 1 case the tumor extended in the mid-brain, and in 1 other case the tumor was predominantly metencephalic.

The survival times measured from the first identifiable symptom or sign are shown in Fig. 1. The average duration from the first symptom to exitus was 17 months. However, this average was distorted by the unusual cases to be discussed. The median survival was 8.3 months, a figure that is more indicative of the usual case. Expressed another way, almost 80 per cent of the patients lived within 20 months of their first symptom, and 90 per cent within 30 months.

The longest survival was 14 years. There were 5 patients who survived 6 years or longer. In 2 of the latter cases, biopsies were performed early in the course. Since they are representative of the group, they will be described in detail.

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In 1928, at the age of 37, this right-handed white male had a convulsive seizure lasting a few minutes. Thereafter at intervals of about 2 to 3 months, he had attacks beginning with numbness and twitching of the right hand, then a tonic convolution of the right side and subsequent loss of consciousness. In 1931, following an attack, he noticed loss of sensation on the right side of the body and a right hemiparesis. In 1933 a partial motor aphasia developed.

Operation. Dr. Paul C. Bucy operated on him in October, 1933. A firm area measuring 2 cm. in diameter was found on the left side in the gyrus just anterior to the precentral gyrus. The remainder of the brain in the operative field appeared normal, except for very slight flattening of the convolutions. On incision the tumor was tough, and reddish-gray in appearance. An attempt at complete removal was not made because of the location. A small piece was taken for study, and a temporal decompression performed.

Microscopic Examination. The tissue was diagnosed by Dr. Percival Bailey as a malignant glioma, probably a glioblastoma multiforme. The slide was studied by us and this diagnosis confirmed. It should be emphasized that many mitotic figures were present. Fig. 2 illustrates the character of this neoplasm.*

Course. Following the operation, the patient was given a course of roentgen therapy for a total of 6,068 r. and was placed on phenobarbital. For the next 4 years he was free of convulsive attacks. His control over the right side of the body improved, and he was able to write and use tools. He gained in weight and general health. In September, 1937, he was struck by an automobile, and was unconscious for 24 hours. Sometime thereafter his seizures returned. He gradually lost power on the right side, and aphasia became worse.

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* We are indebted to Dr. Theodore Rasmussen for permission to examine the slides and reproduce the picture.
In October, 1939, he was seen by Dr. Leo Davidoff. At this time the findings were those of right-sided weakness, slightly hyperactive deep reflexes on the right, and a concave left temporal decompression. An encephalogram was interpreted as showing left-sided cerebral atrophy without evidence of regrowth. Nothing further was done.

He entered Montefiore Hospital in August, 1940 at the age of 49. In addition to the above findings there were now astereognosis in the right hand, a partial motor aphasia, and some blurring of the right disc margin. The CSF contained 3 cells, with 52 mg. per cent protein. The Wassermann test was negative. During his stay in the hospital, both focal motor and generalized seizures were noted. Irradiation was not deemed advisable, and he was discharged to be followed in the out-patient clinic.

He had increasing difficulties in expressing himself. Because of this, he insisted on being re-admitted in July, 1941. At this time it was felt that the paretic side was more spastic, and that the motor aphasia now had a sensory component. CSF examination, including cells, protein, and pressure, were within normal limits. He was given a course of roentgen-therapy amounting to 3,000 r. with slight improvement. Thereafter he continued to have right-sided seizures until July, 1943, when he rapidly became worse and died. A lumbar puncture 5 days before death revealed a pressure of 560 mm. of water.

Autopsy. A broncho-pneumonia was found to be the immediate cause of death. The brain weighed 1,420 gm. The left hemisphere was slightly larger than the right.
The frontal convolutions were flattened. There was a hemorrhagic tumor nodule, measuring 3 x 2 cm., in the left 3rd frontal convolution. Other small hemorrhagic nodules were seen in the left precentral gyrus and the superior temporal gyrus. The cerebellum and brain stem were shifted slightly to the right. Section of the frontal lobes disclosed a large hemorrhagic and necrotic neoplasm (Fig. 3). It measured 5

by 3 cm. and involved both white and gray matter. The left lateral ventricle was constricted and pushed to the right. The tumor disappeared from view when the basal ganglia were reached, but there was swelling of the white matter throughout the left hemisphere. The left putamen contained a hemorrhagic cyst. The cortical architecture in the left premotor convolutions was distorted.

*Microscopic Examination.* The tumor was a glioblastoma multiforme. There were some spongioblastic portions, but there were, in addition, extensive necrosis, pseudopalisading around focal necrotic zones, thrombosis of vessels and endothelial proliferation, perivascular lymphocytes, numerous mitotic figures, and pleomorphism (Fig. 4).

*Comment.* This patient had a histologically malignant neoplasm at the time of his operation. This was equally true of the tumor seen at autopsy. The length of survival is, to the best of our knowledge, the longest on record in a proved case of glioblastoma multiforme.

**Case 2. B.K. Autopsy #10,210. Onset with vomiting, dizziness, and alteration of voice. Operation 1 year later with removal of cerebellar astrocytoma. Death with autopsy 7 years after onset. Glioblastoma multiforme.**

In 1938, at the age of 24, the patient, a right-handed white female, experienced "morning sickness." After awaking, she would vomit a small amount of green fluid and then felt better. Several weeks later, she noticed dizziness occurring 2 or 3 times a week. This was associated with a feeling of unsteadiness in the legs, and a tendency to fall to the right. These bouts lasted about 10 minutes. At this time, her voice changed, and there was occasional gasping. The morning vomiting, dizziness, and

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*Fig. 3. Case 1. Coronal section through the frontal lobes. The neoplasm is hemorrhagic, the left hemisphere swollen, and the midline shifted. Nissl stain.*
voice difficulties became steadily worse. In September, 1938 her right foot began to drag. In November she had difficulty using her right hand and arm. Swallowing difficulties supervened and regurgitation of food occurred. In December she entered a hospital where the CSF was at a pressure of 140 mm., and the Wassermann, colloidal gold and globulin tests were negative. A right recurrent laryngeal paralysis was found. The clinical diagnosis was a posterior fossa lesion. She was found to be pregnant and was aborted in January, 1939.
Operation. In February, 1939 a craniotomy revealed a cerebellar and brain stem neoplasm, which was biopsied.

Microscopic Examination. A diagnosis of astrocytoma was made. The diagnosis was confirmed at this hospital.*

Course. Her speaking and swallowing improved, but the dizziness and vomiting continued. She received a course of x-ray therapy and was admitted to Montefiore Hospital in July, 1939. Here she was given further x-ray therapy and discharged to be readmitted in June, 1942. At that time she stated that she had been able to get about fairly well, except that 2 months prior to admission, swaying and weakness increased. Another series of radiation treatments was given. Her final admission was in July, 1945, when she entered complaining of severe occipital headaches and some diminution of vision. Examination at this time showed the presence of cerebellar signs on the right, and palsies of the right 3rd, 6th, and 7th cranial nerves. Her course was then progressively downhill. She became cyanotic, comatose, and died in July, 1945.

Autopsy. Examination was limited to the nervous system. Externally, the neoplasm was seen in the right cerebellar hemisphere and the right side of the pons and medulla. On sectioning the brain, the corpus callosum was enlarged and contained numerous cysts. The right side of the pons was replaced by a white, firm tumor with

* We wish to thank Dr. Joseph Felsen for permission to examine these slides.
no sharp boundary between it and normal tissue. There was extension of the tumor to the left side of the pons. The neoplasm in the right cerebellar hemisphere was hemorrhagic. A separate neoplasm of similar appearance was present in the left cerebellar hemisphere.

Microscopic Examination. The cysts in the corpus callosum were astrocytic. The cerebellar and pontine neoplasms were typical glioblastoma multiforme (Fig. 5).

Comment. In this case it was less certain that a malignant neoplasm was present from the onset. It was possible that the biopsy was taken from the edge of a deeper-lying, more malignant glioma. Another interpretation was that a more benign neoplasm became malignant spontaneously, or following operation and irradiation. It is not possible to determine which alternative explanation is correct. Nevertheless what is deemed a malignant neoplasm histologically may sometimes be compatible with a relatively long survival. Case 1 represents more certain evidence of this.

DISCUSSION

The following factors have been considered as possible aids in determining survival in cases of glioblastoma multiforme.

1. Age of Onset. The longest survivals (6 years or more) all occurred in patients whose age at onset was from 24 to 42 years. There were many others, however, in this age range who had only the usual brief survival period. None of the older nor the younger patients had a long survival. It should be noted that the peak of the age-incidence curve of glioblastoma is at 50–60 years.

2. Sex. There is a definitely higher incidence of glioblastomas in males. This had been found by many others, see for example, Busch and Christensen. Because of the higher incidence, the question was asked whether survival was shorter in males. In this series there was no significant difference in the average survival time of the two sexes.

3. Initial Symptoms. The average survival of all patients was 17 months. In 13 patients in whom a motor seizure of any type was the first symptom, the average duration was 39 months. If the seizure was focal motor in character (9 cases), the average survival was lengthened to 51 months. Unfortunately, the focal seizure was not uniformly indicative of greater length of survival. Table 1 demonstrates that 3 of the 9 patients in this group had a survival around the general average. There was nothing in the succeeding course that could be correlated with length of survival. Bailey and Cushing reported 5 of 77 cases with survival of over 3 years from the onset of symptoms—3, 4, 6, 6, and 12 years. They commented that "the longest survival periods all prove to be ones with a premonitory history of Jacksonian seizures for many years before pressure symptoms supervene." While this was not invariably true in our long-surviving cases, longer life with this initial symptom is a striking fact. The Montreal group reported 3 cases with long survival and an early history of focal epilepsy. It is not clear why this should be true. Since operation appears to have
little effect on longevity (see below), it cannot be explained by the fact that a seizure brings the patient sooner to the neurosurgeon.

4. Operation. In 57 of 70 cases, operation was performed. A variety of types of internal and external decompressions were done. Symptoms were present an average of 7.1 months before operation, and the average post-operative survival was 10.7 months. Therefore, the average survival from the first symptom was 17.8 months, although the median was 13.9 months. The average duration of non-operated cases was 12 months. The average duration of all cases in the series was 17 months. It therefore appears that operation alone does not significantly increase longevity. Decompression may afford the patient more comfort but life is not prolonged.

TABLE 1
Survival in Cases with Focal Motor Seizure as the Initial Symptom

<table>
<thead>
<tr>
<th>Patient</th>
<th>Survival from First Symptom in Months</th>
<th>Location of Tumor</th>
<th>Number of Operations</th>
<th>Postoperative Survival in Months</th>
<th>Irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>S.S.</td>
<td>168</td>
<td>Left F-P</td>
<td>2</td>
<td>120, 12</td>
<td>Yes</td>
</tr>
<tr>
<td>H.K.</td>
<td>81</td>
<td>Right T-P</td>
<td>2</td>
<td>24+, 12+</td>
<td>Yes</td>
</tr>
<tr>
<td>F.K.</td>
<td>74</td>
<td>Right T-P</td>
<td>2</td>
<td>49, 7</td>
<td>Yes</td>
</tr>
<tr>
<td>A.S.</td>
<td>48</td>
<td>Left F-T-P</td>
<td>3</td>
<td>18, 18, 7</td>
<td>Yes</td>
</tr>
<tr>
<td>G.S.</td>
<td>24</td>
<td>Left T-P</td>
<td>1</td>
<td>24</td>
<td>Yes</td>
</tr>
<tr>
<td>L.S.</td>
<td>20</td>
<td>Right F-P</td>
<td>1</td>
<td>17</td>
<td>Yes</td>
</tr>
<tr>
<td>M.M.</td>
<td>18</td>
<td>Right F-T-P</td>
<td>2</td>
<td>18, 11</td>
<td>Yes</td>
</tr>
<tr>
<td>C.C.</td>
<td>14</td>
<td>Right F-P</td>
<td>1</td>
<td>6</td>
<td>Yes</td>
</tr>
<tr>
<td>N.K.</td>
<td>13</td>
<td>Left F-T-P</td>
<td>1</td>
<td>4</td>
<td>No</td>
</tr>
</tbody>
</table>

Note: The location in H.K. and F.K. was determined by biopsy only. H.K. is alive at the present time. All other patients in this group came to necropsy.

5. Irradiation. Among the 57 patients operated upon, 35 received radiation postoperatively. The details of therapy were so varied that it would be futile to subdivide them. The average survival from the first symptom, in the irradiated group, was 27 months, median 13.1. The average survival in the non-irradiated group was 8.8 months, median 6.2. Within the latter group, however, were so many cases in which death occurred in the immediate and later postoperative period that the average gives a false impression. Thus, eliminating those patients who died within 1 week after operation, the average survival of non-irradiated patients is raised to 12 months. It appears that patients who live longer have more opportunity to be irradiated rather than the reverse. The effect of the usual course of irradiation on longevity is slight.

6. Location. An attempt to correlate longevity with location of the tumor within the cerebrum yielded no significant results. This in part may have been due to the predominance of autopsy cases in this series, since in these cases there was time for extensive growth prior to death.
7. **Histology.** There have been a few recent attempts to correlate survival rates with subdivisions of the group of glioblastoma multiforme as devised by Bailey and Cushing. In our experience these subdivisions are difficult to use. The subtypes overlap, both in the same case and in different cases. The multiform aspect of the glioblastoma is such that if a large number of sections be taken, all varieties of cellular and vascular changes may be found.

**SUMMARY AND CONCLUSIONS**

In a series of 70 verified cases of glioblastoma multiforme, a greater proportion of males to females was found in the ratio of 1.8:1. Five patients survived 6 years or longer from the time of the first symptom, the longest being 14 years. An analysis of factors in survival revealed that operation had no significant effect on longevity; irradiation a slight effect, if any. The longest survivals occurred in patients with onset at from 24 to 42 years of age. However, age at onset was not a constant prognostic factor. The sex of the patient, the location of the neoplasm, or the histologic appearance gave no indication as to longevity. A significant lengthening of survival was found in those patients whose initial symptom was a focal motor seizure. While this was generally true, some patients with this symptom had a short survival. At the present time, there is no means, clinical or histologic, of predicting in a given case which patient will survive longer than the average.

The possibility is considered that in certain cases, an originally benign neoplasm becomes malignant and is seen as a glioblastoma multiforme at autopsy.

It is suggested that in reporting survival in cases of neoplasms of the nervous system, the survival from the first symptom as well as the post-operative survival be given.

Mr. Antol Herskovitz prepared the photomicrographs.

**REFERENCES**