Malignant glioma of the brain-stem
A clinicopathological analysis of 13 cases

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SUMMARY Thirteen cases of malignant glial tumours of the brain-stem that came to necropsy have
been analysed in detail. These patients followed a rather uniform course defined by the early onset of
signs and symptoms of increased intracranial pressure, poor response to radiotherapy, and short
total duration of illness. Pathological features were also similar in all cases, with each tumour showing
areas ranging from benign to frankly malignant. This regional variability points to the limited usefulness
of small biopsies and also indicates the need for complete necropsy studies. The term 'spongioblastoma polare' should probably be avoided, and it is suggested that the histological classification
of glial brain-stem tumours be similar to the classification of such tumours elsewhere in the neuraxis.

Primary intraaxial glial tumours of the brain-stem occur fairly frequently in children (Bray,
Carter, and Taveras, 1958; Panitch and Berg, 1970) and, although they are also found in adult
life (White, 1963), the relative incidence as compared with extraaxial posterior fossa tumours is
somewhat lower, leading to increased difficulties in diagnosis. A significant percentage of these
tumours have the histological characteristics of malignant gliomas or glioblastoma multiforme,
rather than appearing like the so-called spongioblastoma polare (Bassoe and Apfelbach, 1925;
Buckley, 1930; Horrax and Buckley, 1930; Hare and Wolf, 1934; Alpers and Yaskin, 1939; Bray
et al., 1958; White, 1963; Lassman and Arjona, 1967; Panitch and Berg, 1970). In every large
reported series great variations in clinical course, length of survival, and response to treatment are
seen. There is, however, no agreement as to whether evidence of histological malignancy affects these clinical parameters (Lassman and Arjona, 1967; Panitch and Berg, 1970).

Despite this relatively frequent occurrence of malignant tumours, no author has analysed
critically the clinical characteristics of this particular group. The present series of cases of
malignant tumours of the brain-stem suggests that they form a definable clinical and patho-
logical subgroup with its own clinical characteristics, course, and response to treatment. The clinically malignant course is present from the beginning and does not represent an acceleration of a more indolent pattern. It should be possible, therefore, to make the diagnosis of a malignant
tumour early in the course of the illness in the majority of cases, allowing therapeutic and
prognostic decisions to be based rationally.

METHODS
Thirteen necropsied cases of malignant brain-stem glioma from the records of the Department of
Neurology and the Neuropathology Laboratory of the Montefiore Hospital and Medical Center were
studied. The clinical charts were reviewed in detail as were radiographs and other special studies where indicated. One patient died without hospitalization, and limited clinical data are available.

Adequate sections from various levels of the brain-stem and other pertinent areas of the nervous system
were available for study. The sections were prepared from celloidin or paraffin embedded tissue and were
stained by haematoxylin and eosin, Nissl, Woelcke, and phosphotungstic acid haematoxylin (PTAH)
techniques. Special attention was given to the site and
extent of the tumours, as well as to their gross and microscopic appearance.

RESULTS

The ages of the patients form a bimodal distribution, the children having a mean age of 6·5 years (9 months to 11 years); the adults, 44·6 years (30 to 56 years). There is a slight preponderance of males (8:13).

Signs, symptoms, or radiological evidence of compromise of the cerebrospinal fluid pathways were frequent features (Table). Seven patients had at least two such stigmata, and three of them exhibited three or more.

<table>
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<tr>
<td>INCREASED INTRACRANIAL PRESSURE</td>
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<tr>
<td>Papilloedema</td>
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<tr>
<td>Headache</td>
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<tr>
<td>Nausea and vomiting</td>
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<tr>
<td>Ventricular dilatation</td>
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<td>Non-filling ventricular system</td>
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The neurological signs are summarized in Fig. 1. Seven patients had cranial nerve abnormalities among their presenting complaints. These consisted of facial weakness in two, facial numbness in two, vertigo in two, and tinnitus in one.

Abnormalities of ocular motility were present in all cases. Six patients had diplopia at the onset of symptoms and one child had a head tilt. During the course of the illness every patient examined manifested at least two of the three signs of extraocular muscle palsies, gaze paralysis, and pathological nystagmus. Eight patients had gaze palsy, rotatory nystagmus or vertical nystagmus, cardinal signs of intrinsic brain-stem involvement.

Skull radiographs and electroencephalograms contributed little to the diagnosis. In one case, an enlarged acoustic meatus on x-ray examination, in association with the clinical findings of a cerebellopontine angle syndrome, led to an incorrect diagnosis of acoustic neurilemmoma. Spinal fluid protein was measured in nine patients and was elevated in five with levels ranging from 59 to 147 mg/100 ml.

The total duration of the illness, dated from the onset of symptoms, was quite short (Fig. 2). The average life span of the children was 4·3 months (2·5–8 months) whereas it was 10·3 months (1–26 months) in the adults. If the one long-term survivor in the adult group is excluded, the mean survival time was 6·3 months. The median survival time for children was 3 months and for adults, 8·5 months.

Ten patients received radiotherapy, either
with or without prior suboccipital decompression and exploration. Three of these died during treatment, often with a sudden and severe increase in signs and symptoms. The seven patients finishing the planned course of radiotherapy (3500 r or greater) had a mean survival time of 3-6 months after treatment with a maximum of eight months. The three untreated patients survived for an average of 2-7 months with a maximum of five months.

**FIG. 3.** Glioblastoma involving the left side of the pons and partially occupying the cerebellopontine angle. The basilar artery lies in a deep groove on the midline.

**FIG. 4.** Glioblastoma involving the left side of the pons with rostral infiltration into the left side of the midbrain. The fourth ventricle is obstructed. The position of the median raphe is indicated by arrows.

**FIG. 5.** Major pathological features.
The neuropathological features, both in children and adults, were found to be similar. The tumours in all cases were present in the pons with predominantly unilateral involvement in nine patients and bilateral diffuse involvement in four, resulting in asymmetrical (Fig. 3) or symmetrical enlargement of the pons respectively. In cases showing predominantly unilateral involvement, the median raphe of the pons could be seen especially on the side of major involvement. In some instances, the proximal portions of the cranial nerves were found to be infiltrated by the tumour. The basilar artery was frequently found to be in a deep groove or in a tunnel formed by encirclement by tumour (Fig. 3). Similarly, tumour outgrowth around the smaller blood vessels resulted in a lobulated appearance of the external surface of the pons (Fig. 3). Occasionally, the basilar artery was slightly displaced laterally as well as ventrally; in most cases, however, displacement of the basilar artery was not significant.

Tumour bulged into the fourth ventricle in all

**FIG. 6.** Infiltrating malignant astrocytoma of the pons. Streaming of the pleomorphic tumour cells in fascicles can be seen. Haematoxylin and eosin, ×140.

**FIG. 7.** Glioblastoma multiforme of the pons showing pseudopalisading and vascular proliferative changes. Haematoxylin and eosin, ×140.
patients, resulting in partial or complete obstruction of the cerebrospinal fluid pathway (Fig. 4). Hydrocephalus of a moderate to severe degree was found in eight cases. In two cases, the tumour protruded into the subarachnoid space, occupying the cerebellopontine angle (Fig. 3).

Histologically, the tumour in each instance was found to be basically composed of cells of astrocytic nature. The cells ranged from readily recognizable fibrillary or protoplasmic astrocytes to undifferentiated bizarre forms and these were found in variable proportions in different areas. The degree of pleomorphism, however, varied from case to case. Utilizing the same histological criteria of malignancy as applied to astrocytomas elsewhere in the central nervous system, the tumours in the present series would be classified as malignant astrocytomas in five cases (Fig. 6) and glioblastoma multiforme in eight cases (Fig. 7). Although in most cases the features of malignancy were present throughout the tumour, two exhibited these features only in small scattered areas likely to be overlooked in limited histological necropsy examination or biopsy.

Regardless of the microscopic histological features, the outstanding characteristic common to all cases was the remarkably infiltrative nature of these tumours. Tumour cells, isolated or in groups, were seen freely infiltrating along the fibre tracts in various directions (Fig. 6). Intact neurones were frequently entrapped in the midst of tumour proliferation. Occasionally, infiltrating tumour was seen in the proximal portions of the cranial nerves (Fig. 8). The tumour cells infiltrating along the course of fibre tracts frequently assumed elongated and relatively uniform shapes with uni- or bipolar processes resembling the so-called spongioblastomas. In the central part of the tumour, however, especially in the tegmental regions, the tumour cells were found to be haphazard in distribution with distinct pleomorphism and appeared as malignant astrocytoma or glioblastoma.

**DISCUSSION**

One of the first well-defined clinicopathological series of gliomas primary to the brain-stem was that of Bassoe and Apfelbach (1925). Although the histological description was limited, one of their four cases may have been a malignant glioma. Horrax and Buckley (1930) described one glioblastoma multiforme in a series of seven brain-stem gliomas; Buckley (1930), 10 out of 25; Hare and Wolfe (1934), three out of seven;
and Alpers and Yaskin (1939), four out of 11. Other authors have presented similar experiences, with a variable but significant number of cases in any one series representing malignant gliomas histologically.

In a recent review of 48 cases of brain-stem tumours in children, histological diagnoses were available in 10; five of these showed varying degrees of glioblastomatous change (Bray et al., 1958). Another paediatric series confirmed 10 of 40 cases as being, histologically, glioblastoma multiforme, or mixed glioma with anaplasia (Panitch and Berg, 1970). White’s (1963) series, restricted to brain-stem tumours in adults, had histological verification in 28 of 44 cases. Seven were classified as glioblastoma multiforme and eight demonstrated glioblastomatous changes arising in an astrocytoma.

The purpose of this report is to analyse critically this histologically malignant subgroup, comparing the findings with the reported series in which histology is either undefined or ignored.

One of the most important clinical features differentiating malignant brain-stem tumours from the more usual slow-growing astrocytomas is the early and striking appearance of signs and symptoms of increased intracranial pressure. This is associated in some cases with papilloedema well before the terminal phase of the patient’s illness. Only two patients in our entire series lacked evidence of ventricular dilatation either on early radiographic studies or at post-mortem examination. It should be noted that six of nine air studies were carried out by the lumbar route, and no mortality or serious morbidity was associated with this procedure.

A second cardinal feature is the rapid and relentlessly progressive course leading to death in approximately four months in the average child and 10 months in the adult group. Only three patients survived for longer than one year.

In a large series of adult patients with brain-stem gliomas (White, 1963) it is possible to perform an analysis of survival correlated with pathology, although this was not done by the author. This reveals that patients with histologically proven glioblastoma or mixed astrocytoma-glioblastoma survived for an average of 8-3 months, while those patients with benign astrocytomas had a mean survival of 30-5 months. Two of the patients in the astrocytoma group were still alive 78 and 120 months after the onset of symptoms.

In a series restricted to children (Panitch and Berg, 1970), patients with benign astrocytomas had symptoms for an average of 17-0 months before diagnosis and survived for an average of 32-4 months after diagnosis was confirmed. The group of patients with ‘mixed glioma with anaplasia’ were diagnosed 3-0 months after the onset of symptoms and survived an additional 6-4 months in the average case. Frank glioblastoma multiforme in other patients was diagnosed 3-0 months after the first symptom, but those patients survived only an additional 2-8 months. The survival times for patients with malignant tumours in both series are, therefore, quite similar to those in our group.

It is likely that the discrepancies in survival time in some other series and the broad range of survival times in individual cases may, therefore, in part be a function of the tumour histology.

Although beneficial effects of radiotherapy have been reported in as many as 67% of cases of pontine glioma (Redmond, 1961) the treatment series also have not been analysed utilizing the additional variable of histological pathology. In the present cases, no patient showed clinical improvement during or after the administration of radiotherapy. Indeed, three patients succumbed during treatment with a marked exacerbation of signs and symptoms. Mean survival time for the patients not receiving any treatment was 2-7 months, while those patients able to finish the prescribed course of radiotherapy (generally 3500 r or more) survived for an additional 3-6 months on the average.

Diagnostic problems arise in the adult group due to the relative infrequency of brain-stem tumours during the adult years of life. This fact, combined with the high incidence of predominantly unilateral long tract signs and the frequent evidence of increased intracranial pressure, compounds the diagnostic difficulty. These difficulties may be further increased by outgrowth of tumour into the cerebellopontine angle with clinical and radiographic findings typical of an angle syndrome.

Elevation of the cerebrospinal fluid protein level also provides a source of diagnostic confusion. It is stated that this value is generally normal in brain-stem tumours (Bray et al., 1958).
Rather than leading one away from the diagnosis, however, an increased level of protein may suggest a malignant histological picture as was seen in five of the nine patients in this series undergoing lumbar puncture.

Another source of potential diagnostic error is in neuroradiological studies. Confusion with cerebellopontine angle tumours both on routine skull radiography and pneumoencephalography has already been noted. In addition, the expected angiographic finding of widening of the brainstem with displacement of the basilar artery towards the clivus is also not predictable, since the tumour frequently grows around the artery, enclosing it in a groove or tunnel without producing displacement. Other arteries may also show minimal or no displacement for the same reasons.

The pathological features of the brain-stem gliomas in the present series were essentially similar to those described in detail by many authors (Buckley, 1930; Hare and Wolf, 1934; Pilcher, 1934; Alpers and Yaskin, 1939; Ingraham and Matson, 1969). Despite the basic histological similarities, there appears to be considerable diversity in the nomenclature of this group of tumours. Thus, a variety of terms such as astrocytoma, spongioblastoma, glioblastoma, or mixed glioma have been used (Buckley, 1930; Hare and Wolf, 1934; Bray et al., 1958; Redmond, 1961; Ingraham and Matson, 1969). A major problem in establishing a satisfactory classification is the wide range of histological variation often seen in different areas of the same tumour. Consequently, histological examination of a limited region of such a tumour at necropsy or surgical biopsy may not reveal its true nature. This may explain apparent discrepancies between the histological type of the tumour and length of survival of patients (Lassman and Arjona, 1967).

Detailed pathological study in this series clearly demonstrated the frequent occurrence of spongioblastoma-like areas in tumours otherwise indistinguishable from malignant astrocytomas or glioblastomas found elsewhere in the central nervous system. Furthermore, there is no uniformity of opinion among neuropathologists regarding the nature and biological behaviour of spongioblastomas (Rubinstein, 1964; Zulch, 1964). Therefore, it is probably best to avoid this term in the classification of brain-stem gliomas. Since these tumours are basically similar to others of the astrocytic series, they should be classified by the same criteria as are applied to similar tumours elsewhere in the central nervous system. Such classification would not only provide uniformity in terminology, but would give a better understanding of their apparently variable expressions in terms of clinical manifestations and prognosis.

The authors are indebted to Dr. H. M. Zimmerman, Chief, Department of Pathology, Montefiore Hospital and Medical Center, for his encouragement and help throughout this undertaking.

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J Neurol Neurosurg Psychiatry 1972 35: 732-738
doi: 10.1136/jnnp.35.5.732