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Brainstem Glioma: An Analysis of 85 Cases

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Summary

The study analyses 85 cases of brainstem glioma in the past 35 years, 69 of which include patients under 16 years of age. The incidence of brainstem glioma was 2.4% of all intracranial tumours, and 9.4% of intracranial tumours in children. There were two peaks in age distribution, in the first and in the fourth decades.

In children, the tumours were located mainly in the pons, so VIth and VIIth cranial nerve palsies, and pyramidal and cerebellar signs were frequently seen. In adult cases, the tumours ranged in location from the midbrain to the medulla, so neurological symptoms caused by lesions of the whole brainstem axis were seen. The left side was dominant in both age groups.

The choice of treatment was steroid administration and radiation. Chemotherapy was not effective. Even after these treatments, the median survival period from onset was no longer than 10.5 months.

We conclude that the treatment of brainstem gliomas in children should be distinguished from adult cases, which in the latter may be considered to be merely one of the gliomas which may occur at any other sites. Since brainstem gliomas in children may be congenital, we must redirect our treatment of these lesions to treatment of congenital tumours.

Keywords: Brainstem glioma; pontine glioma; clinical features; prognosis.

Introduction

Brainstem gliomas occur with an incidence of 1.4% of all intracranial tumours, and comprise 28.7% of posterior fossa tumours in the young[5, 13, 15]. These tumours show typical neurological signs and symptoms and are rather easily diagnosed. They grow diffusely with infiltration into complex tracts and nuclei and, with the exception of exophytic or cystic types[7, 9], are usually inoperable by virtue of their location. In a number of series, radiotherapy with or without chemotherapy was the usual choice of treatment on the basis of the clinical and radiographic findings. Some authors have reported the possibility of increased effectiveness of radiation when combined with adjuvant chemotherapy[8], but survival after this combination of treatments was not prolonged significantly. Since the development of the CT scan, the locations of brainstem gliomas have been evaluated accurately. Although some reports have emphasized surgical indications[3], treatment is generally the same as in the pre-CT era. Therefore, we present a detailed analysis of our experience with brainstem gliomas.

We have encountered 85 cases of brainstem gliomas in the 35 years from 1948 to 1983, and have analysed them, together with a review of the literature, in an attempt to further understand this rare and prognostically grim tumour.

Clinical Materials and Methods

A total of 85 patients with brainstem gliomas were admitted to the Neurosurgical Department, Kyoto University Hospital, during the period between January 1948 and January 1983. The final diagnosis was based on autopsy in 20 cases, on operative specimens in 9 cases, on neuroradiological examination in 48 cases and only on typical clinical symptoms in 8 cases. Nineteen cases were evaluated histologically; 4 were glioblastoma, 4 were astrocytoma grade III, 6 were astrocytoma grade I or II, and 5 were astrocytoma, grade unspecified. Suboccipital craniotomies were performed in 25 cases, half of which included explorations performed before the introduction of the CT scan. Neuroradiological examinations, which included pneumoencephalography, ventriculography, angiography and CT scans, were performed in 77 cases. CT scans were performed on 16 cases since 1976.

These 85 cases were analysed with respect to clinical signs and symptoms, location of the tumours, and survival time.

Results

1. Incidence

The primary brain tumours in these 35 years numbered 3,774 cases, 730 cases of which were in children.

Since brainstem gliomas included 85 cases in the same years, of which 69 cases were in children, the incidence of brainstem gliomas was 2.4% of all intracranial tumours, and 9.4% of all tumours in children.

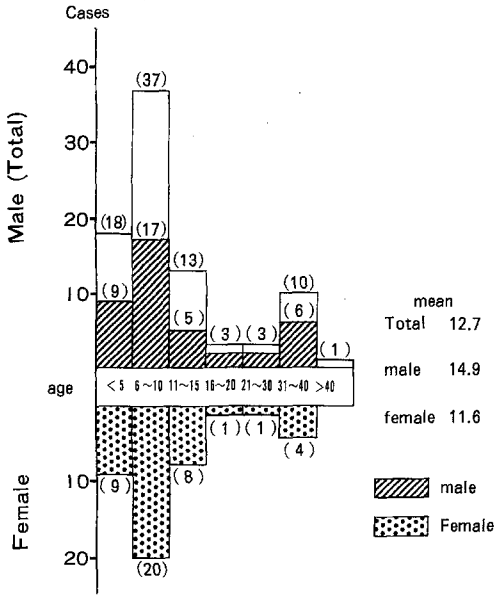

Fig. 1. Age and sex distribution

2. *Age and Sex Distribution*

Of the 85 cases, 42 were male and 43 were female. The ages ranged from one year to 57 years; 69 cases were below 16 years and 16 cases over 16 years of age. There were two peaks of distribution, one in the first and the other in the fourth decade. The sex differences between these age distributions is shown in Fig. 1, which shows female predominance in children and male predominance in adults.

3. *Initial Symptoms and Prediagnostic Duration of Illness*

The most frequent initial symptom was gait disturbance which was due to either hemiparesis or cerebellar disorders. This was followed by headache, nausea and vomiting, visual disturbance due to sixth nerve palsy, hearing disturbance, vertigo, and dysarthria as shown in Fig. 2. Visual disturbance, headache, and nausea and vomiting were more frequent in children. In contrast, gait disturbance, hearing disturbance, vertigo, dysarthria and dysphagia were more common in adults.

The mean duration of symptoms before admission was 5.48 months (the median value was 3 months) ranging from 14 days to 4 years. In adults only, the mean duration was 10.6 months (the median value was

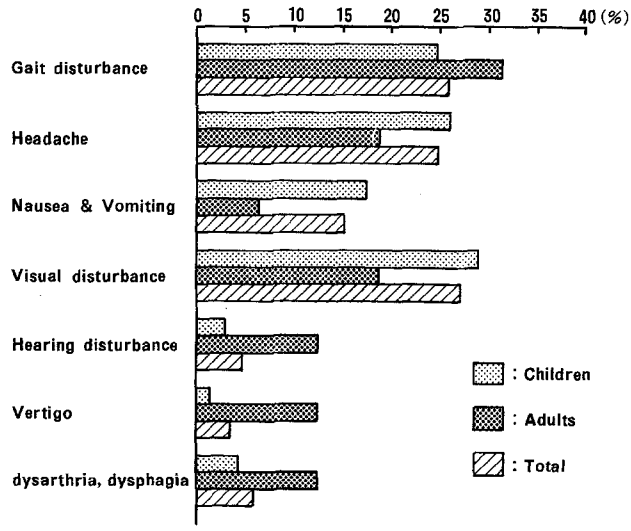

Fig. 2. Initial symptoms

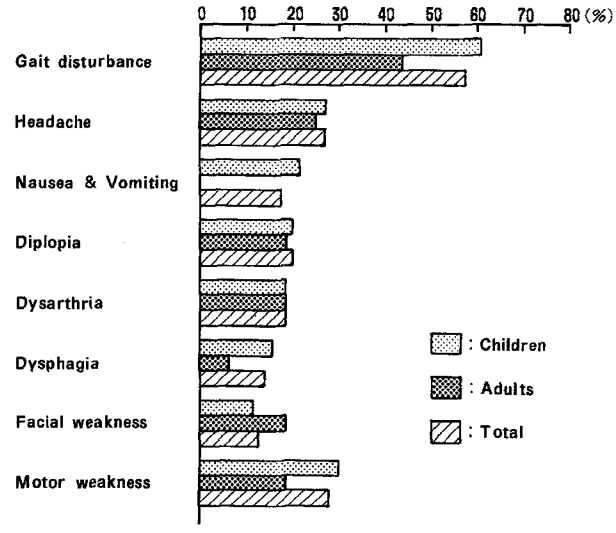

Fig. 3. Symptoms on admission

4 months), but the difference from the total group of patients was not significant.

4. *Subjective and Objective Findings on Admission*

The most frequent initial symptom was gait disturbance which was due to either hemiparesis or cerebellar ataxia, followed by headache, diplopia, dysarthria with dysphagia and vomiting, personality changes, and vertigo. Gait disturbance and diplopia were common in children, while personality changes were more frequent in adults (Fig. 3).

The distribution of neurological findings on admission is shown in Fig. 4. More than half of the cases showed either pyramidal signs, abducens or facial

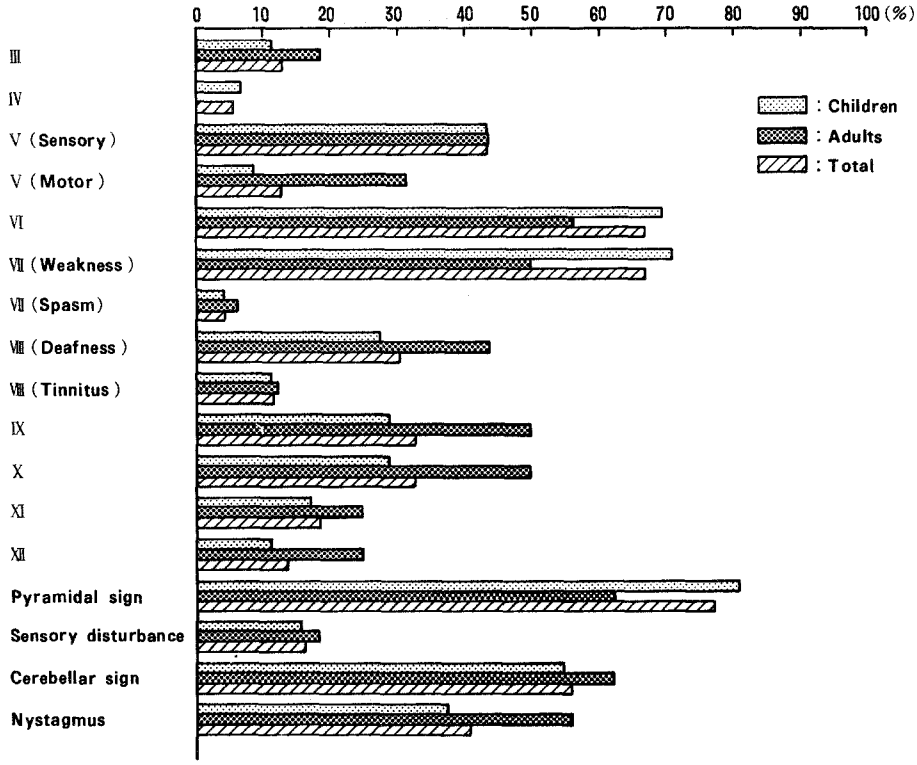

Fig. 4. Neurological findings on admission

palsies, or a cerebellar disorder. In children, pyramidal signs were more common than facial nerve palsies. In contrast, lower cranial nerve palsies were more common in adults.

5. Neuroradiological Findings

CT scans were performed in 14 cases, while the remaining cases were diagnosed by typical neurological symptoms and pneumoencephalography or a positive contrast ventriculography. In most cases, these contrast studies revealed dorsal or lateral displacement of the aqueduct of Sylvius. Two cases showed exophytic extensions angiographically.

In thirteen cases the CT revealed a low density relative to the normal brain parenchyma and diffuse enlargement of the brainstem. After contrast enhancement, two thirds of the cases showed no increase in density, while one third of cases showed ring-enhancement (Fig. 5). One case showed diffuse homogeneous enhancement. Another case showed a slightly high density area on the plain CT and no enhancement. In the latter case, acute deterioration and death occurred within one month after the diagnosis was made (Fig. 6).

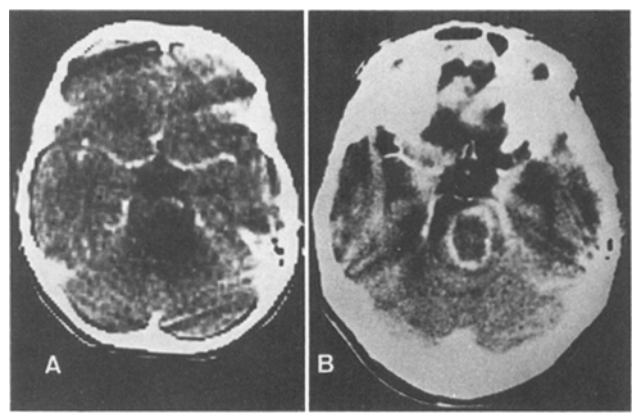

Fig. 5. Computed tomography after contrast enhancement of two typical cases. A) Nonenhancing brainstem glioma, B) ring-enhancing brainstem glioma

6. Localization and Laterality (Fig. 7)

According to the neurological signs and symptoms, or findings of neuroradiological studies on admission, all brainstem gliomas were divided into three sites: those with lesions near the midbrain (cephalad), those with lesions in the pons, and those with lesions near the medulla (caudad). Furthermore, each site was divided into three locations, including right, left, and bilateral.

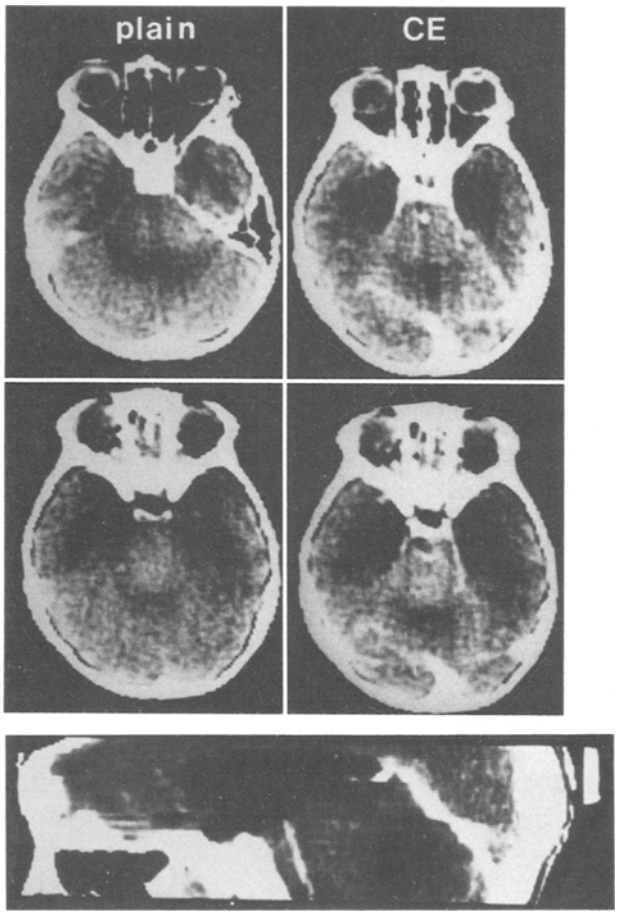

Fig. 6. Computed tomography of patient showing acute deterioration. Slightly high density in the plain CT and no enhancement after contrast study

In children, the tumours were restricted to the pons in over 70% of cases, caudad extensions occurred in 17% and cephalad tumours were noted in 8.7%; twice as many tumours were found on the left than either the right side or bilaterally.

In adult cases, tumours were noted to be more cephalically and caudally distributed. Thirty one per cent of the tumours were located mainly in the medulla with 12% in the midbrain. As in children, the left side was most frequently involved.

7. Treatment and Prognosis (Table 1)

We analysed a total of 70 cases which had resulted in death. Some deaths occurred immediately after examinations such as Moljodol ventriculography and others occurred immediately postoperatively. These cases were excluded from the following analysis. Of the remaining 55 cases, the mean and median survivals from onset to death were 13.9 and 10.5 months, respectively. Median survival from hospital admission to death was 7.0 months. With brainstem gliomas, there may be little difference between the day of admission and the day of the beginning of treatment. In adults, median survival from onset to death was 12.5 months, which was slightly longer than that of the children.

All of the 55 patients received a tumour dose of 4,000–5,000 rads fractionated over 5–7 weeks and nine patients died before completion of irradiation. Thirty patients received radiation therapy alone.

The other 25 patients received steroid hormones. The dose of steroids was variable in each case. Eighteen of these patients showed remarkable improvements in neurological deficits immediately after administration of steroid hormones.

Eight of the 25 patients treated with both radiation and steroid hormones also received adjuvant chemotherapy in a combination of vincristine, cyclophosphamide and adriamycin. Recently, intraarterial injection of ACNU {3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-1-(2-chloroethyl)-1-nitrosourea hydrochloride}, "Nimustive Hydrochloride", has also been administered in 3 cases.

Two patients received radiation with adjuvant chemotherapy without steroid hormones. The median survival time from onset in the cases with radiation therapy alone was nine months, but that in cases with both radiation and steroids was 10.5 months. We were unable to prolong survival times by adjuvant chemotherapy.

There were many cases in which steroid treatment resulted in remarkable improvements of neurological deficits after hospital admission, but survival times in these cases were not prolonged compared with the other cases.

Since the introduction of the CT scan, we have experienced 10 cases of brainstem gliomas with survival similar to cases diagnosed prior to CT. Survival times of four cases showing ring enhancement in the CT were a little shorter than the other cases.

Discussion

Brainstem gliomas predominate in children, especially in those from six to ten years of age. A second peak is seen in the fourth decade in adults. There are few reports about the differences in these tumours between children and adults[4, 11]. Some authors reported that brainstem gliomas in adults are more frequent than previously expected[16]. Other authors reported the neurological signs and symptoms associated with brainstem gliomas, and concluded that there are no

		Right	Bilateral	Left	Total
Children	Midbrain	1	2	3	6(8.7)
	Pons	15	12	24	51(73.9)
	Medulla	2	5	5	12(17.4)
		18(26.1)	19(27.5)	32(46.4)	69(100)
Adults	Midbrain	1	0	1	2(12.5)
	Pons	2	2	5	9(56.3)
	Medulla	2	2	1	5(31.2)
		5(31.3)	4(25.0)	7(43.5)	16(100)
Total	Midbrain	2	2	4	8(9.4)
	Pons	17	14	29	60(70.6)
	Medulla	4	7	6	17(20.0)
		23(27.1)	23(27.1)	39(45.9)	85(100)

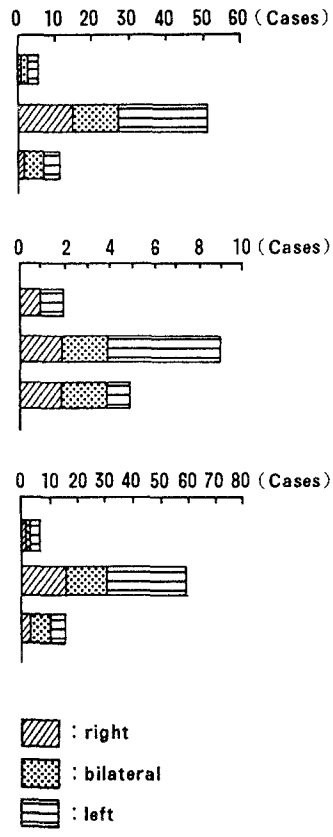

Fig. 7. Localization and laterality

Table 1

	No. of Cases	Time from admission to death (months)		Time from onset to death (months)	
		Mean	Median	Mean	Median
Total	(70)	5.5	4.0	11.2	8.0
Total with early death excluded	(55)	7.0	7.0	13.9	10.5
Children	(42)	7.0	7.0	9.4	8.5
Adults	(13)	6.9	2.5	19.2	12.5
Radiotherapy (R)	(30)	7.4	6.0	12.6	9.0
R + Steroid administration (S)	(17)	7.8	6.0	14.9	10.5
R + S + Chemotherapy	(8)	5.6	6.0	8.9	8.0
Ring-enhancement on CT	(4)	6.5	6.5	8.5	8.0
No enhancement on CT	(4)	7.0	6.5	8.5	7.5

Survival for all evaluable patients.
Upper row: differences between children and adults.
Middle row: differences between the types of treatment.
Bottom row: differences between CT findings.

differences between these two groups. White[16] also reported that there are no significant differences between these two groups, with the exception of more frequent gaze palsies in children. In our series, although the majority of cases display the characteristic neurological signs and symptoms restricted to the pons, some exception were noted; that is, neurological signs and symptoms caused by spread to the midbrain or medulla were noted in adult cases. We suspect that the tumours arising in children are congenital[7] and their origin is constant, on the floor of the IVth ventricle[6]. In contrast, tumours arising in adults may include any of the gliomas arising at other sites, accounting for their inconstant locations. Mantravadi[10] reported some autopsy cases in which brainstem gliomas of the pons showed more malignant features than gliomas of the medulla or midbrain. Thus, typical cases arising in children may show a more rapid clinical course than those of adults.

The CT scan shows two typical findings, a low density area and swelling of the brainstem. In our series, thirteen cases showed low density areas and one case showed an iso- or slightly high density area in the plain CT. The latter case exhibited the most rapid deterioration and death occurred within one month of diagnosis. However, the histological diagnosis was benign astrocytoma, grade II. In this respect, this case was different from Takeuchi's case[14] which revealed a calcified image radiologically, but the histological diagnosis was glioblastoma. After contrast enhancement, the CT may be divided into two groups, nonenhancing or enhancing; the latter group may show either ring enhancement or diffuse enhancement. Bilaniuk[2] reported that the grade of brainstem gliomas contrasts with supratentorial gliomas; in the brainstem, low grade gliomas show heterogeneous enhancement and high grade gliomas reveal a non-enhancing low density area in the CT scan, which is the reverse of the pattern seen in supratentorial gliomas. Hoffman[5] also reported some cases as a distinct group of benign brainstem gliomas, in which the clinical symptoms were atypical and the CT scan showed markedly enhancing lesions, but in which the histological diagnosis was benign astrocytoma. We have not experienced a large number of such cases but the prognosis does not appear to be different in these two groups.

Neurological signs and symptoms were predominantly on the left side in our series, but the low density area in the CT scan did not always correlate with the laterality. Some cases showed typical unilateral brain stem findings on neurological examination but a midline low density area was seen in the CT scan. This may be due to the hypothesis that the low density area seen in the CT is not identical to the site of tumour itself, but may include peritumoral oedema. In the brainstem, oedema may occur more severely than in the cerebrum[12]. This is likely to be the reason that steroid therapy is very effective in ameliorating neurological symptoms at the initial stage.

Statistically, the group which received both radiation and steroid administration showed a little longer survival, but we cannot be satisfied with this small degree of prolongation. Results of the use of chemotherapy have been pessimistic for brainstem gliomas, as in our series and in the reports of Levin[9] or Fulton[3]. We conclude that the treatment of brainstem glioma should be divided into two groups. The first is the tumours arising in children. The treatment of this group should be programmed as follows: first, irradiation and steroids, followed by a review of these treatment modalities. The dose and area of irradiation[11] and the mode of steroid administration must then be considered again. Chemotherapy, which is used for other gliomas at present, is ineffective for brainstem gliomas in children; therefore, we must develop other agents for this particular type of congenital tumours. In the group of tumours arising in adults, the choice of treatment is the same as with other gliomas, including radiation and chemotherapy.

Some authors have emphasized surgical indication. Alvisi *et al.*[1] reported that 6 out of 16 patients which received surgical intervention lived more than 10 years; in contrast, most of the untreated patient died within four months. They also stressed the usefulues of surgical treatment of brainstem gliomas. But age distribution and incidence of the symptoms of intracranial hypertension in the surgically treated group are fairly different from our cases, which may include some differences in patient selection. We conclud that the surgical indication of typical brainstem glioma will be restricted to small tumours, however, we should make an effort to treat surgically thus getting over the pessimism in selected cases.

References

1. Alvisi, C., Cerisoli, M., Maccheroni, M. E., Long-term results of surgically treated brainstem gliomas. Acta Neurochir. (Wien) *76* (1985), 12–17.
2. Bilaniuk, L. T., Zimmerman, R. A., Littman, P., Gallo, E., Rorke, L. B., D. A., Schut, L., Computed tomography of brain stem gliomas in children. Radiology *134* (1980), 89–95.

3. Fulton, D. S., Levin, V. A., Wara, W. M., Edwards, M. S., Wilson, C. B., Chemotherapy of pediatric brain-stem tumors. J. Neurosurg. *54* (1981), 721–725.
4. Golden, G. S., Ghatak, N. R., Hirano, A., French, J. H., Malignant glioma of the brain-stem. J. Neurol. Neurosurg. Psychiatry *35* (1972), 732–738.
5. Hoffman, H. J., Becker, L., Craven, M. A., A clinically and pathologically distinct group of benign brain stem gliomas. Neurosurgery *7* (1980), 243–248.
6. Hoang, Y. S., Diagnostic criteria of glioma of the pons. Brain and Nerve (JPN) *5* (1953), 188–191.
7. Lassiter, K. R. L., Alexander, E., Jr., Davis, C. H., Jr., Kelly, D. L., Surgical treatment of brain stem gliomas. J. Neurosurg. *34* (1971), 719–725.
8. Levin, V. A., Edwards, M. S., Wara, W. M., Allen, J., Ortega, J., Vestnys, P., 5-Fluorouracil and 1-(2-Chloroethyl)-3-cyclohexyl-l-nitrosourea (CCNU) followed by hydroxyurea, misonidazole, and irradiation for brain stem gliomas: A pilot study of the brain tumor research center and the children's cancer group. Neurosurgery *14* (1984), 679–681.
9. Littman, P., Jarret, P., Bilaniuk, L. T., Rorke, L. B., Zimmerman, R. A., Bruce, D. A., Carabell, S. C., Schut, L., Pediatric brain stem gliomas. Cancer *45* (1980), 1294–1296.
10. Mantravadi, R. V. P., Phatak, R., Bellur, S., Liebner, E. J., Haas, R., Brain stem gliomas: An autopsy study of 25 cases. Cancer *49* (1984), 1294–1296.
11. Ryoo, M. C., King, G. A., Chung, C. T., Yu, W. S., Sagerman, R. H., Irradiation of primary brain-stem tumors. Radiology *13* (1979), 503–507.
12. Sarkari, N. B. S., Bickerstaff, E. R., Relapses and remissions in brain stem tumours. Brit. Med. J. *2* (1969), 21–23.
13. Strange, P., Wohlert, L., Primary brain stem tumours. Acta Neurochir. (Wien) *62* (1982), 219–232.
14. Takeuchi, K., Yokota, H., Konishi, Y., Omata, K., Uchigasaki, S., Akai, K., A pontine glioma showing a calcified image radiologically—A pontine glioblastoma—like tumour associated with a chondrosarcoma. Acta Neurochir. (Wien) *64* (1982), 243–251.
15. Vinken, P. J., Bruyn, G. W., Handbook of Clinical Neurology, Vol. 17, Chap. 19. Lassman, L. P.: Tumors of the pons and medulla oblongata, pp. 693–706. Amsterdam: North-Holland Publishing Company.
16. White, H. H., Brain stem tumors occurring in adults. Neurology *13* (1963), 292–300.

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