BRAIN STEM GLIOMA, A CLINICO-RADIOLOGICAL STUDY: A CLASSIFICATION SYSTEM WITH "PROGNOSTIC SIGNIFICANCE" IS SUGGESTED

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SUMMARY

In the present study 21 patients with the clinico-radiological diagnosis of brain stem glioma are included (13 males and 8 females). Patients were subjected to (1) Full clinical examination (2) MRI and/or CT scan of the brain with and without intravenous contrast enhancement. CT myelography was also done to patients presented with cervicomedullary gliomas. According to the duration of symptomatology before clinical presentation, the anatomical localization of the brain stem gliomas (diffuse versus focal, cystic versus sold), the pattern of contrast enhancement (non, diffuse, ring or patchy enhancement), the pattern of response to radiotherapy and the overall prognosis during a one year follow up, patients were classified into five groups. Group (1) patients with diffuse brain stem gliomas and with a relatively better prognosis (10 patients, 47.5%), group (2) patients with diffuse brain stem gliomas and with a relatively worse prognosis (4 patients, 19%), group (3) patients with focal pontine or midbrain gliomas (4 patients, 19%), group (4)

patients with cervicomedullary gliomas (2 patients, 9.5%) and group (5) a single patient (5%) with probable brain stem metastasis. The clinical and radiological findings in the various groups will be presented and discussed. Lines of treatment, done to each group, and the result of a one year follow up will also be presented and discussed.

INTRODUCTION

Brain stem gliomas are not a homogeneous group of tumors in so far as the anatomical sites, the clinical picture, the radiological findings, the pathological data, and the prognosis are concerned. Accordingly although the prognosis is quite unfavorable, in brain stem gliomas, however it is quite variable from one patient to anther. The variability in prognosis is undoubtedly influenced by the heterogeneity of this uncommon neoplasm. Because of the heterogeneity of this neoplasm, management of patients is best tailored according to fixed clinical, radiological or pathological criteria according to which the patients can be classified into groups. The aim of this study is to look for clinical, radiological or pathological criteria that can separate patients into homogeneous groups with common findings. Groups that share common biological behavior of their tumours and common prognosis and according to which management can be tailored. Groups that can help us better understand the natural history of this neoplasm, hoping to be more capable of helping those miserable patients with brain stem gliomas.

MATERIAL AND METHOD

In the present study 21 patients with the clinico-radiological diagnosis of brain stem glioma are included (13 males and 8 females). Patients were subjected to:

1. **Full clinical examination.**

2. **MRI and/or CT scan of the brain with and without intravenous contrast enhancement. CT myelography was also done to patients presented with cervicomedullary gliomas. The upper cervical spinal cord and the brain stem was studied, by CT myelography, in those patients.**

Following establishment of the diagnosis of brain stem gliomas, all patients were subjected to radiotherapy. The patient with focal cystic pontine glioma was treated with CT guided stereotaxic surgery as will be explained later.

RESULTS

According to the duration of symptomatology before clinical presentation, the anatomical localization of the brain stem gliomas (diffuse versus focal, cystic versus sold), the pattern of contrast enhancement (non, diffuse, ring or patchy enhancement), the pattern of response to radiotherapy and the overall prognosis during a one year follow up, patients were classified into five groups

Group (1) Comprised patients with longer duration of symptomatology before clinical presentation (mean duration of 1.2 years), moderate clinical disability, diffuse brain stem gliomas and no contrast enhancement (10 cases, 47.5%). Radiotherapy in those patients probably retarded the rate of clinical deterioration but did not result in any noticeable improvement of the pre-existing neurological disability. All patients were alive and at least with the base line clinical disability at one year follow up. See table 1

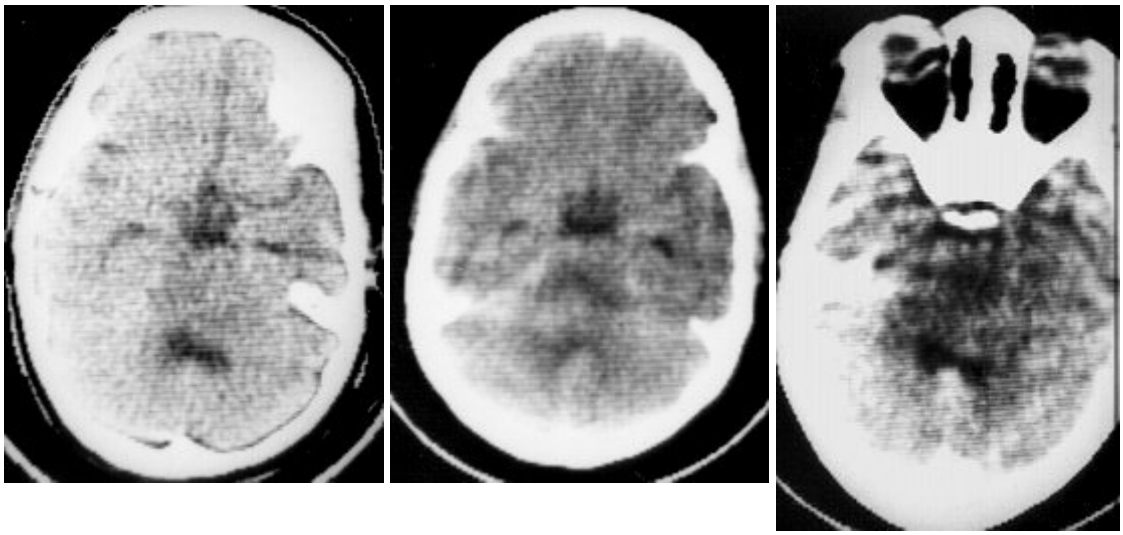
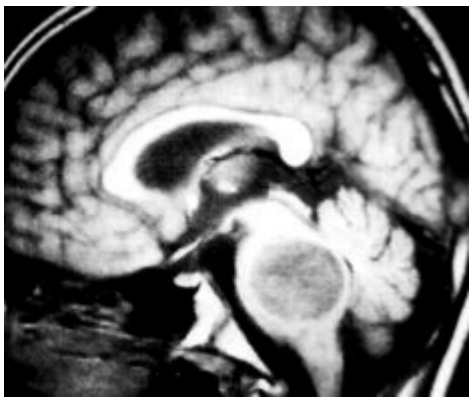


Figure [1] **Precontrast CT scans showing examples of diffuse brain stem gliomas with variable CT densities. The 4th ventricle is compressed and displaced posteriorly. (Group 1,2)**



Group (2) Comprised patients with shorter duration of symptomatology before clinical presentation (mean duration of 4.3 months for patients 11,12,13), severe clinical disability, diffuse brain stem gliomas and patchy or ringlike contrast enhancement (4 patients, 19%). However in patient number 14 (see table 2) the disease started 4 years before clinical presentation and was mainly in the form of horizontal gaze palsy, about five months before clinical presentation the disease rapidly progressed to involve the facial nerves and bulbar cranial nerves, and ultimately the patient became quadriplegic and markedly disabled.

Figure [2A] **For comment see figure 2b**

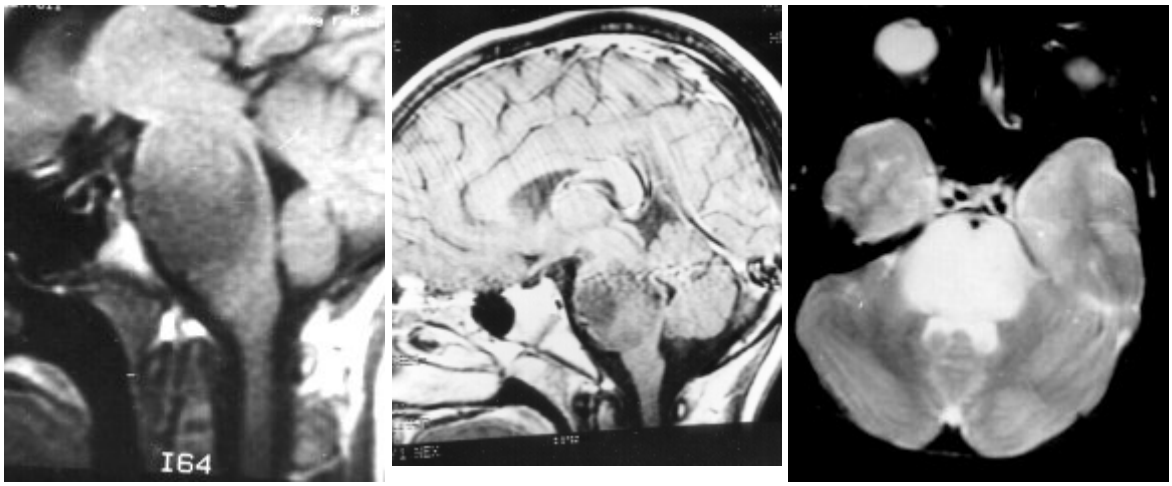
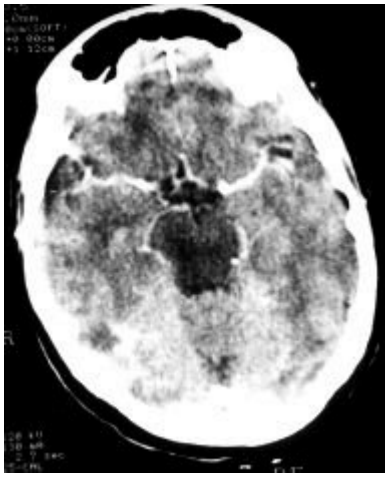


Figure [2 A,B] **Precontrast MRI T1, T2 images showing examples of diffuse brain stem gliomas. The tumours are hypointense on the T1 images and diffusely hyperintense on the MRI T2 images (right images), the main bulk of the tumours is pontine in location. The basilar artery is encased by the tumour (right image) The 4th ventricle is compressed and displaced posteriorly. (Group 1,2)**



In this particular patient the tumour appeared as a non-enhanced focal pontine space occupying lesion on CT scan and MRI T1 images with posterior exophytosis, however the MRI T2 images demonstrated punctate T2 hyperintensities scattered in the pons and the midbrain and apparently radiating from the focal pontine lesion. Disease history for patients number 11,12,13 was very short while that of patient number 14 was composed of two main phases (an initial phase of long duration, during which the disease was very slowly progressive and did not result in significant disability and a second phase of short duration and very rapid clinical progression that ultimately ended in significant disability). All patients, in this group, died during hospitalization, either before (one patient) or immediately after (three patients) initiation of radiotherapy. See table 2

figure [3A] For comment see figure 3B

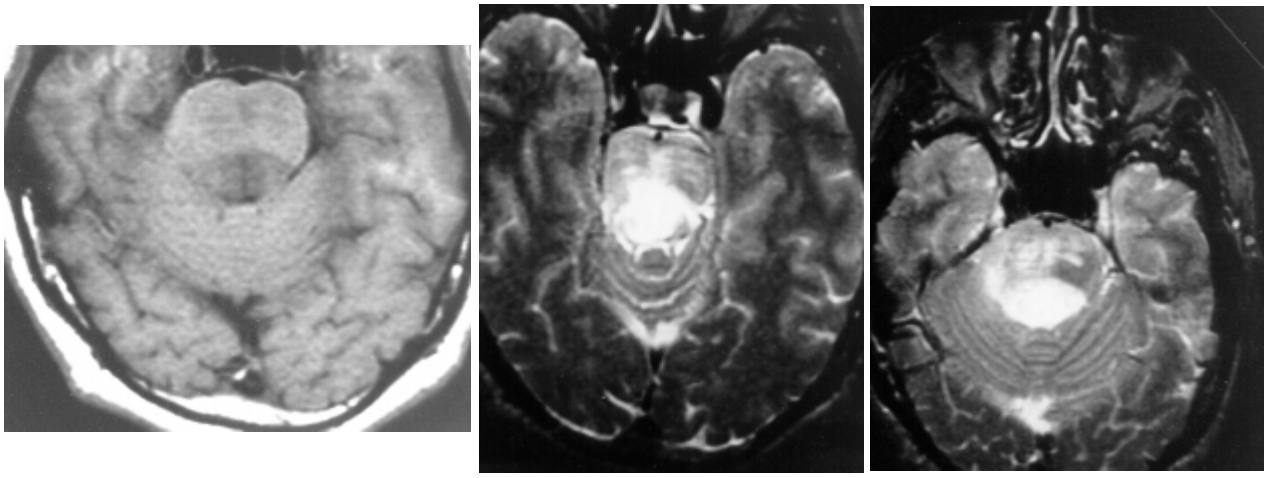


Figure [3A,B] Postcontrast CT scan (figure 3A) and MRI T1, T2 images (figure 3B) showing case number 14, group (2). The focal pontine glioma is of mixed density with posterior exophytosis on CT scan. The tumor is hyperintense on the MRI T2 images and hypointense on the T1 images. Notice the punctate T2 hyperintensities infiltrating the surrounding tissues and apparently radiating from the focal tumour.

Group (3) Comprised patients patients with longer duration of symptomatology before clinical presentation (mean duration of 1.7 years), moderated clinical disability, focal brain stem gliomas (solid or cystic), and intense and diffuse tumour enhancement (4 cases, 19%). Tumours were located in the midbrain (2 patients, 9.5%) or the pons (2 patients, 9.5%). In one patient with focal pontine lesion, the lesion was focally bulging posteriorly into the 4th ventricle (posterior exophytosis) and hydrocephalus was present in this case, while in the other patient with focal pontine lesion, the pontine lesion was cystic, excavating much of the pons with a large mural nodule.

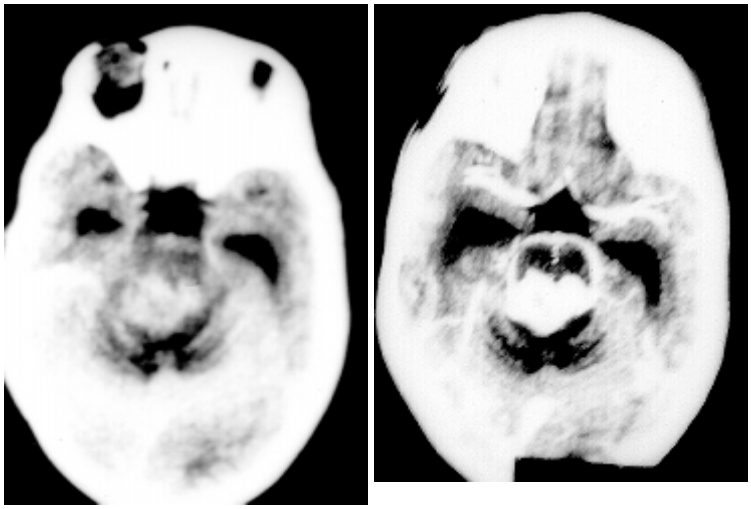


Figure [4] Pre and postcontrast CT scans showing a focal pontine glioma. The tumour is slightly hyperdense on precontrast scan (left) with dense and uniform enhancement on postcontrast scan (right image). Notice the dilatation of temporal horns and posterior exophytosis of the tumour. Case number 18, group (3)

In one patient with midbrain glioma, the tumour extended into the thalamus and induced hydrocephalus. Radiotherapy and/or stereotaxic decompression of the lesion resulted in dramatic improvement of the clinical disability and complete disappearance of the lesions on follow up neuroimaging studies. The two patients with hydrocephalus were shunted before radiotherapy. All patients were alive and almost symptoms free at one year follow up. See table 3

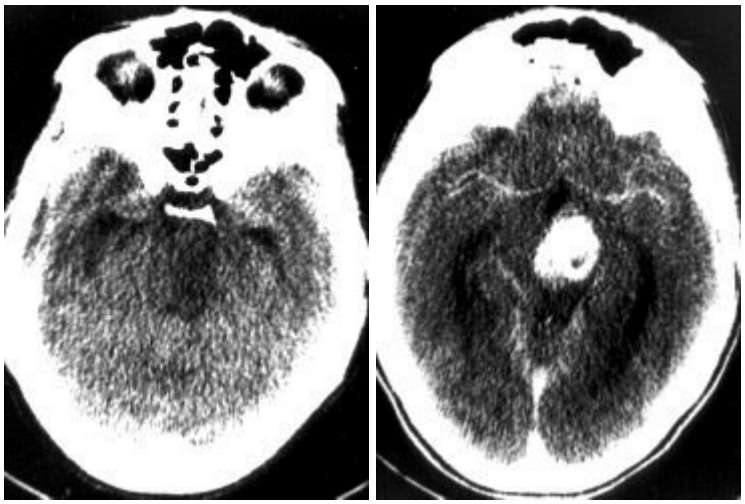


Figure [5] Pre and postcontrast CT scans showing a focal midbrain glioma. The tumour is hypodense on precontrast scan (left image) with dense enhancement on postcontrast scan (right image). Case number 16, group (3)

Group (4) Comprised patients with cervicomedullary gliomas (2 cases 9.5%). Medullary symptomatology followed the spinal symptomatology in all patients by a mean period of (3.6 years). Medullary symptomatology was mild and detected mainly by careful clinical examination. Radiotherapy in those patients probably retarded the rate of clinical deterioration but did not result in any noticeable improvement of the pre-existing neurological disability. All patients were alive and at least with the base line clinical disability at one year follow up. See table 4

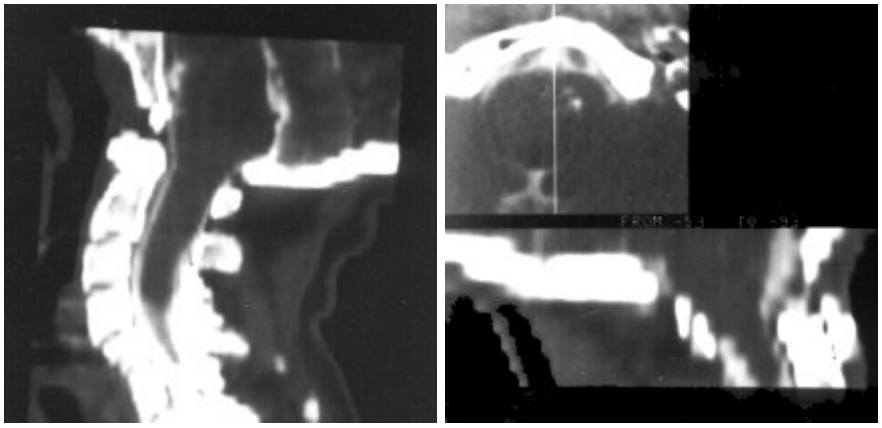


Figure [6] **CT myelography showing two examples of cervicomedullary gliomas. Calcification is present in the right image (was also present in plain CT scan in this patient). Group (4) patients.**

Group (5) Comprised only one case (5%). This patient presented clinically with two focal spinal lesions (in the conus-epiconus region and the region of cervical enlargement) and a focal midbrain lesion inducing left partial third nerve palsy with right sided ataxia. CT myelography (with an early and a late study done 6 hours later) demonstrated cystic intramedullary space occupying lesions in the conus and the lower cervical regions, the lesions were inducing gross asymmetric bulgings in the spinal cord.

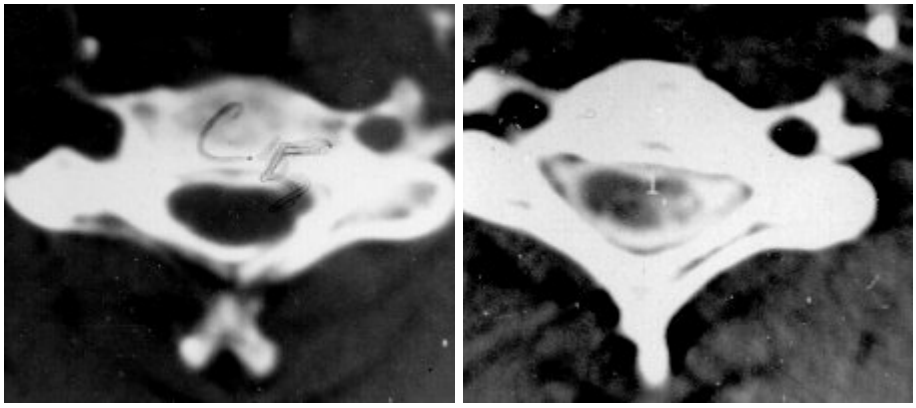


Figure [7] **Lower cervical CT myelography with early study (upper left) and late study (upper right), notice the asymmetric bulging of the spinal cord and the cystic breakdown. Group (5) patient.**

Brain stem radiological examination (CT scan and MRI), in group (5) case, demonstrated a focal left sided midbrain space occupying lesion bulging into the prepontine cistern through the right crus cerebri. This patient was operated upon 9 months earlier for bronchogenic carcinoma. The patient's condition rapidly deteriorated and he died 4 days following hospital admission. Clinical diagnosis was ? spinal cord and brain stem metastasis.

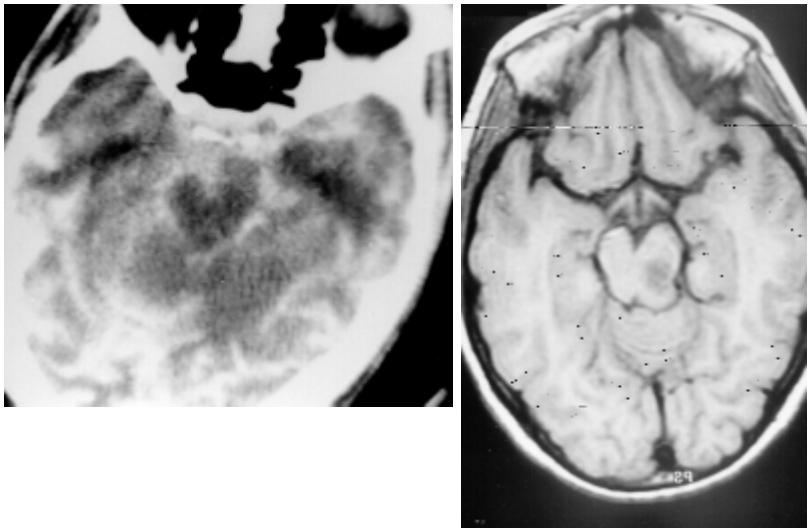


Figure [8] CT myelography (left image) and MRI T1 image (right image) showing a focal left-sided midbrain lesion. Group (5) patient.

Table (1) Patients belonging to group (1)

N	Age	Sex	Clinical picture	CT scan	MRI
1	16	M	Bilateral pyramidal manifestations, mild facial, abducent nerve palsies, no evidence of papilledema, no headache, the condition is gradual and progressive. Unilateral hearing loss was reported by two cases (case number 3,7)	The lesions are diffusely isodense to brain tissues, diffusely enlarging the brain stem. The 4TH ventricle is compressed and displaced posteriorly. No evidence of contrast enhancement.	All lesions are hypointense of the MRI T1 images and diffusely hyperintense of the MRI T2 image. The basilar artery is seen completely encased by the tumours on the MRI T2 images in all cases. The brain stem is diffusely enlarged by the tumour and in many cases the main bulk of the tumours are situated in the pons. The 4TH ventricle is compressed and displaced posteriorly in all cases. No evidence of contrast enhancement.
2	13	F			
3	6	M		The lesions are diffusely hypodense to brain tissues, diffusely enlarging the brain stem. The 4TH ventricle is compressed and displaced posteriorly. No evidence of contrast enhancement. See figure (1,2)	
4	14	F			
5	9	M		All lesions are of mixed density, diffusely enlarging the brain stem. The 4TH ventricle is compressed and displaced posteriorly. No evidence of contrast enhancement.	
6	11	M			
7	14	F			
8	15	F			
9	16	M			
10	10	M			
mean	12.4	-			

Table (2) Patients belonging to group (2)

N	Age	Sex	Clinical picture	CT scan	MRI

11	5	F	Bilateral spastic paraparesis, bilateral horizontal gaze palsy, bilateral bulbar manifestations, vertigo, 7th and sensory 5th affections. The condition is gradual and progressive with no evidence of increased intracranial pressure.	All lesions are of mixed density on precontrast scans, diffusely enlarging the brain stem. The 4TH ventricle is compressed and displaced posteriorly. Patchy enhancement is seen in cases 11,12 and ring enhancement is seen in case 13.	All lesions are hypointense of the MRI T1 images and diffusely hyperintense of the MRI T2 image. The basilar artery is seen completely encased by the tumours on the MRI T2 images in all cases. The brain stem is diffusely enlarged by the tumour and in many cases the main bulk of the tumours are situated in the pons. The 4TH ventricle is compressed and displaced posteriorly in all cases. The pattern of enhancement seen in CT scan is also seen on MRI T1 images.
12	7	F			
13	51	M			
14	42	M		A dorsally exophytic focal space occupying lesion is seen in the posterior part of the pons with no contrast enhancement. The lesion is of mixed density on precontrast CT scan.	The focal pontine lesion is hypointense on the MRI T1 images and hyperintense on the MRI T2 images. Punctate T2 hyperintensities are seen anteriorly in the pons and midbrain. No evidence of contrast enhancement.
mean	26.3	-	-		

Table: Patients belonging to group (3)

Number	Age	Sex	Clinical picture	CT scan	MRI
15	39	F	limitation of vertical gaze and increased intracranial pressure, followed by long tract affection.	Densely and diffusely enhanced focal midbrain lesion extending into the thalamus, with bilateral dilatation of the lateral ventricles.	The midbrain focal lesions are hypointense on the MRI T1 images and hyperintense on the MRI T2 images. The lesions are densely and diffusely enhanced after contrast injection
16	19	F	Unilateral partial third nerve palsy and contralateral ataxic hemiparesis	Densely and diffusely enhanced focal midbrain lesion.	
17	11	M	Moderate clinical disability, unilateral facial nerve palsies, 6th	A huge cystic pontine lesion with a large mural nodule, No contrast enhancement.	A huge cystic pontine lesion with a large mural nodule. No contrast enhancement.
				Densely and diffusely	The posterior pontine focal

18	9	M	nerve palsies vertigo followed by cerebellar manifestations, mild bilateral pyramidal manifestations,	enhanced focal pontine lesion with posterior exophytosis. The lesion is slightly hyperdense on precontrast scans. Hydrocephalus is present in this case.	lesion is hypointense on the MRI T1 images and hyperintense on the MRI T2 images. The lesion is densely and diffusely enhanced after contrast injection
MEAN	19.5	-		-	

Table: Patients belonging to group (4)

Number	Age	Sex	Clinical picture	CT scan	MRI
19	15	M	Bilateral pyramidal manifestations, Horner's syndrome, unilateral mild sensory 5th nerve affection, mild unilateral hypoglossal nerve affection. The condition is gradual and progressive with no evidence of increased intracranial pressure	CT myelography showing enlargement of the upper cervical spinal cord extending upward into the medulla. Calcification is present in one case.	Not done
20	24	M			The tumour is hyperintense on the MRI T2 images and hypointense on the MRI T1 images.
MEAN	19.5	-			

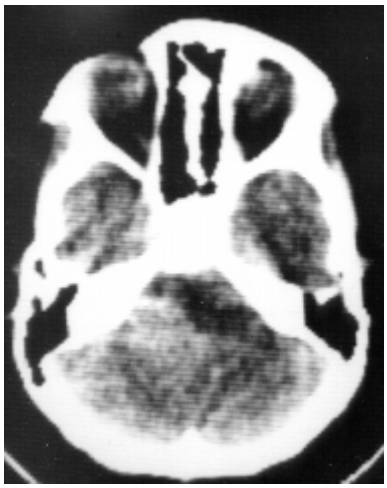
It is interesting to note that the clinical picture was mainly focalized in the pons in patients with diffuse brain stem glioma (group 1,2) and radiologically, although the tumours were seen diffusely enlarging the brain stem, they were also mainly localized in the pons in many of these patients. Midbrain symptomatology was not observed in any patient belonging to groups (1,2) and medullary symptomatology was not observed in any patient belonging to group (1). Medullary symptomatology was quite florid in group (2) patients and was correlated with bad prognosis and they followed pontine symptomatology in all group (2) patients. In general group 2 patients, in comparison to group 1 patients, are characterized by abundance of cranial nerve palsies. Manifestations of increased intracranial pressure were absent in all patients except in two case (patients number 15, 18, group 3), see table 3. In focal midbrain glioma patients (patients number 15, 16 group 3) the clinical picture was localized to the midbrain and symptomatology caudal to the midbrain was not seen in any patient.

It must also be mentioned that the clinical picture in group 1, 2, 3 patients actually started with cranial nerve dysfunctions (in the form of 3rd, 7th, 5th, 6th, bulbar cranial nerve palsies or vertigo etc.) or gaze palsies (horizontal or vertical) and cranial nerve dysfunctions and/or gaze palsies dominated the clinical picture on presentation. Long tract affection followed, clinically, cranial nerve dysfunctions in all group 1, 2, 3 patients and was less prominent compared with cranial nerve dysfunctions in those patients.

Although all tumours were diffusely enlarging the brain stem in group (1) patients, however all

these patients were suffering from moderate clinical disabilities and they were fully ambulant and independent, that is in contrast to all group (2) patients who were markedly disabled and wheel chair confined on admission. In group (3) patients all "CT scan focal brain stem tumours" were also "focal" when examined by MRI. However in case number 14, group (2), although the lesion was seen "focal" by CT scan and MRI T1 images, however MRI T2 images demonstrated punctate T2 hyperintensities diffusely infiltrating the brain stem and radiating from the focal lesion i.e. what appeared "focal" on CT scan turned out to be "diffuse" on MRI especially on the T2 images.

Precontrast neuroimaging studies in group 1,2 showed that the diffuse brain stem gliomas were diffusely isodense(2 cases, 14% of cases with diffuse brain stem gliomas), diffusely hypodense (2 cases, 14% of cases with diffuse brain stem gliomas) or of mixed densities (10 cases, 72% of cases with diffuse brain stem gliomas) on precontrast CT scan. In general these lesions appeared hypointense on the precontrast T1 MRI images and diffusely hyperintense on the T2 MRI images.



Precontrast CT density or MRI signal intensities apparently had no effect on the overall prognosis in those patients. However punctate, rather than diffuse, MRI T2 hyperintensities and patchy or ringlike contrast enhancement were correlated with bad prognosis in this study. It looks like that contrast enhancement in diffuse brain stem glioma is of bad prognostic significance. Contrast enhancement occurred in 3 cases (21% of cases with diffuse brain stem gliomas), all of which belonged to group (2). See table 1,2

Figure [9] Postcontrast CT scan showing a case with brain stem glioma and with patchy enhancement (group 2)

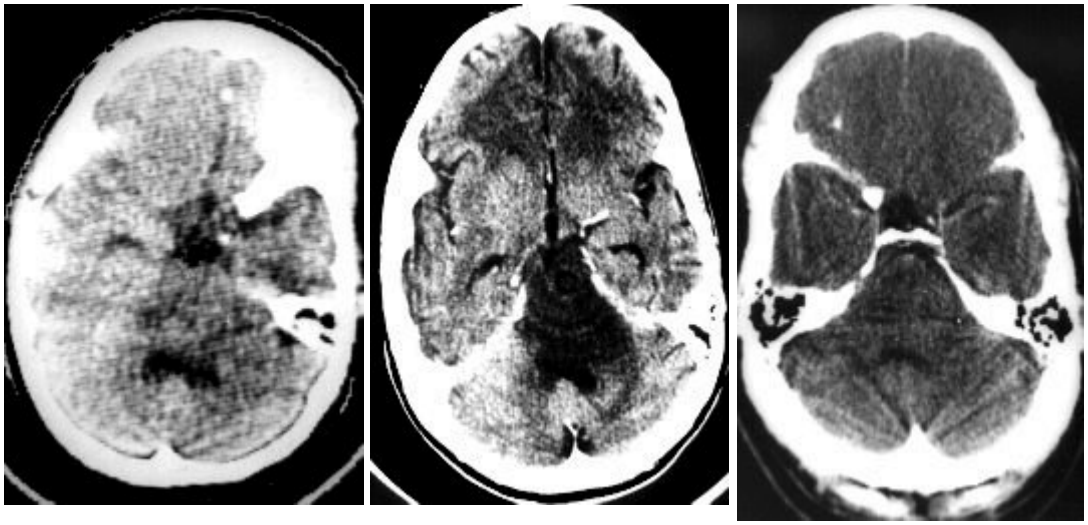


Figure [10] Precontrast CT scan showing examples of diffuse brain stem gliomas. The middle one is diffusely hypodense and the two images on the right and left sides are isodense. The 4th ventricle is compressed and displaced posteriorly. (Group 1,2)

The single patient with focal cystic pontine glioma (case number 17, group 3) was treated by CT guided stereotaxic excision of the mural nodule and decompression of the pontine cyst. Histopathological examination of the excised pathological specimen showed a juvenile pilocytic astrocytoma. All other patients were treated with radiotherapy and subsequently histopathological confirmation is not available in any of them. Postmortem examination was not

done to any patient.

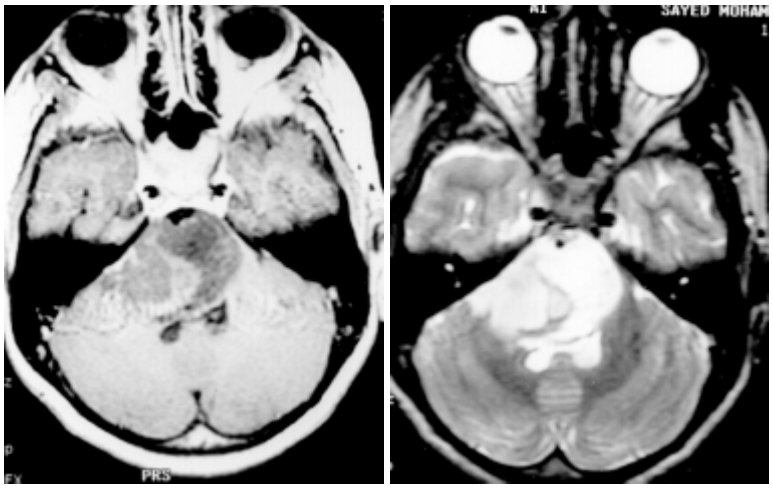


Figure [11] Precontrast MRI T1, T2 images showing a case with focal cystic pontine glioma. Notice the large mural nodule. The 4th ventricle is compressed and displaced posteriorly. Case number 17, group (3)

A summary on the five groups are present in table 5

Table [5] A summary on the five groups

GROUP	Description	Number of cases	%	Duration *
1	Diffuse brain stem glioma with a better prognosis	10	47.5	1.2 YEARS
2	Diffuse brain stem glioma with a worse prognosis	4	19%	4.3 MONTHS
3	Focal brain stem glioma	4	19%	1.7 YEARS
4	Cervicomedullary glioma	2	9.5	3.6 YEARS
5	? Metastatic brain stem lesions	1	5%	3 DAYS

*** Duration here refers to duration of symptomatology before clinical presentation**

DISCUSSION

Intrinsic brain stem tumours have traditionally been treated with irradiation and adjuvant chemotherapy with little success. The neurological course may be transiently improved but then it invariably progresses after a short remission with a dismal outcome. The advent of modern neuroimaging techniques allowed us to visualized the interior of the brain stem and it became obvious that brain stem tumours are heterogeneous and can be classified into groups based on clinical, anatomical and neuroimaging results that when integrated can influence our decision making regarding management of those patients.

In the present study most of brain stem gliomas were of the diffuse type (14 patients, 67%, groups 1, 2) and the brain stem was diffusely enlarged in all these patients, however in patient number 14 (group 2) the brain stem was not diffusely enlarged but rather diffusely infiltrated by the tumour. Contrast enhancement separated patients with diffuse brain stem glioma into two groups from the prognostic point of view (groups 1,2). Contrast enhancement in diffuse brain stem glioma, was coupled with a very bad prognosis (group 2). Albright et al, 1986, Luh and Roger Bird, 1999

Diffuse brain stem gliomas without contrast enhancement (group 1) had an indolent and a very slowly progressive course and although the mean duration of symptomatology for patients

belonging to group (1) was 1.2 years, some of those patients had a duration of symptomatology of over 3.5 years before clinical presentation and when presented clinically they were, in general, moderately disabled by the brain stem tumours. In fact this indicates that brain stem gliomas, in group 1 patients, had a lower grade of malignancy on one hand and on the other hand they were not causing extensive destruction or extensive functional disturbances of the brain stem. Unilateral hearing loss was reported by two cases in group (1) and this was reported before, Albright et al, 1983, Luh and Roger Bird, 1999, it is either vascular in nature (the basilar artery was encased by the tumours in all cases and it is possible that the internal ear blood supply is compromised in this way), Luh and Roger Bird, 1999, Smirniotopoulos, 1999, or it may be due to compression of the cochlear nerve by possible anterolateral exophytosis of the brain stem tumour into the cerebellopontine angle and this was reported before. Albright et al, 1983, Luh and Roger Bird, 1999, It is extremely unlikely that unilateral hearing loss is due to a central brain stem cause. Luh and Roger Bird, 1999, Smirniotopoulos, 1999

From the histopathological point of view low grade brain stem gliomas consist of relatively normal-appearing astrocytes, but there are just too many of them. In the past, this appearance created the impression of some type of developmental or hamartomatous change. They are not characterized by any significant vascular changes, and those that occur are limited to the capillaries. The tumors derive their nutrition from the preexisting normal vessels. Because the vessels are normal, the blood- brain barrier is intact. Mitosis, hemorrhage, vascular proliferation, endothelial changes, anaplasia and necrosis are notably absent in these neoplasms. The lesion infiltrates through the brain, usually by following the path of white matter tracts and the infiltrated brain stem is diffusely expanded and hypercellular. These tumors often may spread through the brain without causing destruction or functionally significant damage, so that symptoms are not an early feature. Albright et al, 1983, Zulch, 1986, Gajjar et al, 1997, Smirniotopoulos, 1999

In low grade astrocytomas, the brain stem can be extensively infiltrated before any symptoms occur. These tumours widely spread without neural destruction or interruption of normal function. Albright et al, 1983, The very slow rate of growth of these tumours allows the brain to move functionality from one region to anther and this process of brain remapping, which has been shown to occur at all ages, is partially responsible for the relatively late appearance of symptoms in low grade diffuse brain stem astrocytomas. Smirniotopoulos, 1999

Radiologically low grade gliomas are usually identified by diffuse enlargement of the brain stem, abnormal signal intensity on MR or abnormal attenuation on CT. The lesions typically have precontrast CT attenuation and MRI signal changes suggesting increased water content and lower than normal specific gravity (lower CT scan densities with MRI T1 hypointensities and diffuse MRI T2 hyperintensities). Hueftle et al, 1985, Lee et al, 1985, It is tempting to consider that these changes represent edema. The question then arises: Is this vasogenic edema or cytotoxic edema? Because the blood-brain barrier is intact in these tumors, vasogenic edema is unlikely. The cells are not dead or dying, so that cytotoxic edema is also unlikely. Perhaps the edema results from the increased number of astrocytic cells that spread apart the normal myelinated axons of the white matter. The presence of significant amount of normal appearing astrocytes results in total increase in the water content of the brain stem. These cells may merely have different physical and chemical properties than the normal tightly packed bundles of axons that traverse through the brain stem. Smirniotopoulos, 1999, As the blood brain barrier is intact in low grade brain stem astrocytomas (grade II astrocytomas according to the WHO), no significant enhancement occurs, either on MRI or CT scan. Enhancement is characteristic of the more aggressive anaplastic astrocytomas (grade III) or glioblastoma multiforme. Bradac et al, 1983, Hueftle et al, 1985, Lee et al, 1985, Ginsberg et al, 1998, Smirniotopoulos, 1999

This is consistent with our findings since the protracted long course of group (1) patients is indicative of tumours with a lower biological activity and the very short disease history in group

(2) patients is indicative of tumours with a higher biological activity. Highly malignant gliomas (glioblastoma multiforme) are characterized by mitosis, necrosis, anaplasia and vascular endothelial hyperplasia. The newly formed blood vessels have abnormal endothelium and often form glomeruloid balls. They are virtually freely permeable and without a blood brain barrier. Highly malignant gliomas induce significant and early destruction of neural tissues and this is responsible for the early appearance of clinical symptomatology in group (2) patents. The presence of blood vessels without a blood brain barrier is responsible for the contrast enhancement observed in highly malignant brain stem gliomas. Burger and Green, 1987, Smirniotopoulos, 1999 Consistent with the findings of Burger and Green, 1987, Smirniotopoulos, 1999, enhancement was characteristically patchy, irregular or ringlike in group (2) patients in this study. The enhanced rings observed in one patient in group (2) were irregular, of variable thickness and with shaggy inner margins and this is characteristic of glioblastoma multiforme. Burger and Green, 1987, Epstein and Wisoff, 1990, Smirniotopoulos, 1999

Glioblastoma multiforme can arise de novo or as a malignant transformation of diffuse low grade astrocytomas. Burger and Green, 1987, Epstein and Wisoff, 1990, Because the mean duration of symptomatology is only a few months in patients number 11,12,13 (group 2) and all these patients were completely normal before onset of symptoms, it is possible to say that malignant gliomas arised de novo in those patients. However the situation is different for patient number 14 (group 2). In this patient the disease started 4 years before clinical presentation and was mainly in the form of horizontal gaze palsy (for which the patient compensated by head turning to either side) and about five months before clinical presentation the disease rapidly progressed to involve the facial nerves and bulbar cranial nerves, and ultimately the patient became quadriplegic and markedly disabled. Radiologically the tumour appeared as a non-enhanced focal pontine space occupying lesion on CT scan and MRI T1 images with posterior exophytosis, however the MRI T2 images demonstrated punctate T2 hyperintensities scattered in the pons and the midbrain and apparently radiating from the focal pontine lesion. In this patient it is possible to say that the brain stem tumour started as a low grade focal pontine glioma that ultimately underwent malignant transformation into a glioma with a higher grade.

In patient number 14 the brain stem was not enlarged and the "intra-brain stem" tumour dissemination from the focal pontine lesion could not be appreciated either on CT scan or on MRI T1 images. Also no significant enhancement was observed on either CT scan or MRI. The high T2 contrast between the hyperintense minute and punctate disseminated lesions and the normal brain tissues (with a much lower T2 contrast) can explain why the disseminated "intra-brain stem" lesions were only picked up by MRI T2 images in this patient and this is consistent with the view point of Luh and Roger Bird, 1999, that the MRI T2 images are most sensitive in delineating the full extent of brain stem gliomas. Apparently the disseminated lesions had not, yet, reached a size large enough to induce observable brain stem enlargement, by the time of clinical diagnosis, and actually they killed the patient before doing so.

Although malignant transformation from a preexisting low grade glioma can easily be inferred, in patient number 14, from the change of the disease course from a slowly progressive one into a rapidly progressive and a fatal one, we did not observe any degree of contrast enhancement in this patient. In fact this can be explained by the smaller size of the malignant disseminated lesions. Although contrast enhancement is universal in highly malignant gliomas, Burger and Green, 1987, Epstein and Wisoff, 1990, however contrast enhancement is only observable, radiologically, when the actual volume of the highly malignant glioma is macroscopic (> 1 cm in diameter). Burger and Green, 1987, Epstein and Wisoff, 1990, Smirniotopoulos, 1999

In fact patient number 14 has given us a peculiar chance to understand the natural history of brain stem glioma as this patient can be regarded as a stage between group (1) patients and other patients belonging to group (2) on one hand and group (3) patients on the other hand. There are two different scenarios that can explain the radiological findings in patient number 14 (neoplastic

cells remote from the main bulk of the tumour). (1) neoplastic cells at the periphery of the preexisting low grade astrocytoma continue to be at risk for transformation into the next highest grade of the tumour resulting into progressive infiltration of the tumour into the surrounding tissues. (2) The widened extracellular spaces created by the vasogenic edema (common in highly malignant gliomas) will facilitate malignant gliomas sending cells streaming into the surrounding brain tissues. Ricci, 1999, Smirniotopoulos, 1999

We strongly oppose the view point of Tokuriki et al, 1986, Epstein and Wisoff, 1990 that all diffuse brain stem gliomas are highly malignant gliomas as the biological behavior of the brain stem gliomas, in all group (1) patients with diffuse brain stem gliomas, indicates the very low biological activity and the very slow rate of growth of these tumours that undoubtedly should rank them as low grade gliomas. From the pathological point of view diffuse astrocytomas are neoplasms of widely varying potential that are unencapsulated, poorly marginated and diffusely infiltrate into the surrounding brain. These diffuse astrocytomas appear to form a continuum of both biological and histological aggression. They vary from lesions with almost normal cytology (grade I and grade II astrocytomas) through intermediate stages (grade III, anaplastic astrocytomas) and up to the most aggressive of all human brain tumours (grade IV astrocytomas or glioblastoma multiforme). Ricci, 1999, Smirniotopoulos, 1999, The word diffuse astrocytoma is not synonymous with glioblastoma and is not against the pathological diagnosis of low grade glioma. A low grade glioma (grade II astrocytoma according to the WHO) has a tendency to diffusely infiltrate the nearby neural tissues, however at a much slower rate (compared with glioblastomas) and with a little tendency to induce extensive structural damage or profound functional disturbance. Ricci, 1999

Focal brain stem gliomas (group 3) occurred in four patients in this study (19%). All of them were moderately disabled on presentation and all of them showed a very good response to radiotherapy. In particular patient number 15, with focal midbrain glioma, was diagnosed in 1988 and is currently (year 2000) still being followed up, she is symptoms free with normal radiological findings and this is consistent with the view point of Luh and Roger Bird, 1999, that the five years survival rate of focal midbrain gliomas, properly diagnosed and treated, is 100%. Posterior exophytosis was demonstrated in one case with focal pontine glioma and the tumour appeared to bulge posteriorly into the fourth ventricle. These tumours characteristically arise subependymally, in the midline, in the floor of the fourth ventricle, then they bulge posteriorly into it and might be mistaken for medulloblastomas when large enough. Ricci, 1999, Smirniotopoulos, 1999

It is interesting that the focal pontine tumour, in case number 18, was slightly hyperdense on precontrast CT scans, this could be due to the marked tumour hypercellularity. Increased cell count is known to increase the CT density. Epstein and Wisoff, 1990 Although the focal tumours in cases 15, 16, 18 (see table 3) showed definite enhancement, however the pattern of enhancement was characteristically dense and homogeneous. This pattern of enhancement is characteristic of low grade gliomas and this is unlike the patchy, irregular or ringlike enhancement characteristic of malignant gliomas. Epstein and Wisoff, 1990, In general it must be noted that a truly focal brain stem tumour, as demonstrated by CT scan, is the one that remains "focal" when examined by MRI. MRI examination is essential for the diagnosis of focal brain stem tumours since it is not uncommon for MRI to demonstrate a more extensive neoplasm than CT scan and in such a case the tumour must be reclassified as diffuse. Focal brain stem neoplasms, as demonstrated by CT scan, are more often than not the tip of the iceberg. MRI T2 images is the optimum scanning procedure for demonstrating the full extend of the brain stem neoplasm and is superior to contrast enhanced images. Epstein and Wisoff, 1990, Luh and Roger Bird, 1999

Brain stem juvenile pilocytic astrocytomas were reported before, Epstein and Wisoff, 1990, Luh and Roger Bird, 1999. Juvenile pilocytic astrocytomas are characterized by a large mural nodule of neoplastic tissues and a cyst wall composed of compressed non-neoplastic neural tissues. Epstein and Wisoff, 1990, The mural nodules might or might not enhance in juvenile pilocytic

astrocytomas, however the cyst wall never enhances. Cyst wall contrast enhancement will shift the pathological diagnosis from the low grade juvenile pilocytic astrocytoma into the highly malignant glioblastoma multiforme (necrosis is responsible for cystic changes in glioblastomas). Ricci, 1999, Smirniotopoulos, 1999, In this study neither the cyst wall nor the mural nodule showed any degree of enhancement in case number 17 (group 3), see table 3. Juvenile pilocytic astrocytomas are rarely encountered in the brain stem and it is of interest to report a case with such a pathology (case number 17), this case was surgically confirmed. Although the cystic tumour, in case number 17, was excavating a huge area of the pons it was associated with paucity of clinical signs and a mild clinical disability and this is due to the very benign nature of the pathology and the very slow rate of growth of these tumours. Epstein and Wisoff, 1990

Cervicomedullary gliomas (group number 4) are either tumours arising from the cervicomedullary junction and extending into the medulla and the upper cervical cord or a primary cervical neoplasm extending rostrally into the medulla. Cervicomedullary gliomas are usually low grade gliomas with a good prognosis and they never extend rostral to the medulla. Hueftle et al, 1985, Lee et al, 1985, Albright et al, 1986, Epstein and Wisoff, 1990, In this study two cases with cervicomedullary gliomas (9.5%) are included. Extension of the tumours rostral to the medulla was not observed clinically or radiologically in any of the two patients included in this study. Both MRI and CT myelography demonstrated this kind of neoplasms fairly well and either can be used as the primary diagnostic procedure. Calcification was seen in one patient with cervicomedullary neoplasms and this was linked with good prognosis. Lee et al, 1985, Albright et al, 1986, Luh and Roger Bird, 1999

Certain questions must be addressed, the first one is: " is it possible to understand the natural history of brain stem gliomas by studying and comparing the clinical and the radiological results of the various cases in group 1,2,3,4. the second question is: " is it necessary to have a stereotaxic or an open surgical biopsy for every case with brain stem glioma" and the third question is: " what are the optimum lines of treatment for brain stem gliomas".

In group (1, 2) patients, all cases started by pontine cranial nerve palsies (6th and 7th, horizontal gaze palsy) that were followed by medullary cranial nerve dysfunction (bulbar, hypoglossal, vestibular etc.) in group (2) and this were followed in both group by long tract affection. MRI examination in group (1,2) patients demonstrated that the main bulk of the brain stem tumours is located in the pons. In group (3) patients also the condition started by cranial nerves or gaze palsies in the absence of definite long tract dysfunction. The posterior part of the brain stem is mainly reticular while the anterior part is compact and is occupied mainly by the pyramid. Cranial nerve nuclei and gaze centers are embedded in the reticular (posterior) parts of the brain stem. Metwally, 1995, Peele, 1997, Metwally, 2000, In this way it is possible to say that brain stem gliomas start posteriorly whether focal or diffuse and whether in the pons or midbrain and that in diffuse brain stem gliomas the pathology start focally in the posterior parts of the pons then spread to involve other parts of the brain stem, the magnitude of caudal spread to the medulla is greater because we did not observe midbrain symptomatology in diffuse brain stem gliomas. This medullary spread was linked with poor prognosis (group 2). Albright et al, 1986, Barkovich et al, 1991, This pattern of spread is best demonstrated in case number 14 (group 2) as the condition started as a focal posterior pontine glioma of low grade malignancy then started to spread to other parts of the brain stem later on resulting in a diffuse brain stem glioma.

In this way every diffuse brain stem glioma starts as a focal pontine one. Spread of a focal brain stem glioma, within the brain stem, is not necessarily associated with a change in the grade of that glioma. Transformation of a focal brain stem low grade glioma into a diffuse one will be very slow if the focal tumour retains the same grade of the neoplasm (group 1 patients). However if the focal glioma starts as a highly malignant one or if the focal low grade glioma changes its grade into the highest next grades, then the transformation from a focal tumour into a diffuse one will be very rapid (group 2 patients). A change in the grade of gliomas is more likely to occur at an the older

age. At older age (over the age of 40 years) diffuse low grade astrocytomas have a bad prognosis because they have a great tendency for anaplastic transformation, Albright et al, 1986 while at a younger age anaplastic transformation of diffuse low grade astrocytomas is extremely uncommon, Epstein and Wisoff, 1990, also the probability for diffuse low grade astrocytomas to have a malignant component is higher at the older age and the condition is age dependant. Albright et al, 1986, Barker et al 1997, This is consistent with our findings since the mean age for group (1) patients was 12.4 years and that for group (2) patients was 26.3 years. Group (2) comprised two patients older than 40 years (patients number 13, 14, see table 2).

Unlike focal midbrain gliomas and cervicomedullary gliomas, focal pontine gliomas have a peculiar tendency to diffusely infiltrate the brain stem thus ultimately getting transformed into diffuse brain stem gliomas. Luh and Roger Bird, 1999, It is not known why brain stem gliomas, whether diffuse or focal, start in the posterior parts of the brain stem. Astrocytes are more abundant in the perivascular, subependymal and subpial regions, Peele, 1997, and as explained previously the focal pontine tumours in patients number 14, 18 showed posterior exophytosis and such tumours are believed to arise in the subependymal region forming the floor of the 4th ventricle. Epstein and Wisoff, 1990, It is possible that abundance of astrocytes in the subependymal and posterior parts of the brain stem will provide the fertile soil for the initial growth of astrocytomas. The posterior parts of the brain stem, being more reticular, will yield the least resistance for the cephalo-caudal spread of brain stem tumours and this might explain why in group (2) patients spread of astrocytomas to the medulla was associated with abundance of medullary cranial nerves palsies (posterior parts) and paucity of long tract signs (anterior parts).

Regarding the value of biopsy in brain stem gliomas, this dilemma is best explained in the light of the pathology of brain stem gliomas. Brain stem gliomas are in general diffuse astrocytomas. In practice considerable histological heterogeneity in astrocytic tumours is found (i.e., low grade areas with Rosenthal fibers and calcification can be intermixed with with frankly malignant ones). Paulus and Pfeiffer, 1989, Ricci, 1999, Biopsy specimen, either stereotaxic or open, is usually too small and might miss the tumour regions that contain the most malignant part and subsequently biopsy is useless in so far as tumours grading is concerned, Hood et al, 1986. Tomita et al, 1981 review of autopsy and biopsy data gathered from multiple large series of brain stem gliomas demonstrated significant discrepancies between surgical and autopsy pathology.

In fact we agree with the view point of Hood et al 1986, Luh and Roger Bird, 1999, that biopsy, either stereotaxic or open, is to invasive to be a practical option for brain stem glioma patients unless it is done in the context of surgical debulking of the brain stem tumours as will be explained later. Tumour grading is best inferred from the biological activity of that tumour and the result of neuroimaging studies. Hood et al, 1986, Epstein and Wisoff, 1990, The poisonous snake is the one that rapidly kills when it bites, also the highly malignant brain stem tumours are those that rapidly induce significant neurological disability within a very short period of time. Neuroimaging criteria suggestive of brain stem gliomas and their possible grades were described earlier in this studies. Our openion is consistent with the view point of Hood et al, 1986, Epstein and Wisoff, 1990, that the sensitivity of MRI when combined with the clinical presentation is uniformly diagnostic of brain stem gliomas and their grades and obviates the need to inflect a surgical procedure on an already ill patient just to obtain a small biopsy specimen. Empiric treatment with steroid and radiotherapy are recommended, in brain stem gliomas, unless surgical debulking is an option. Hood et al, 1986, Epstein and Wisoff, 1990, Ricci, 1999

Regarding lines of management of brain stem gliomas, therapy is best tailored according to whether the tumour is focal or diffuse, the anatomical location of the tumour when focal and the possible tumour grade (as judged clinically and radiologically) as follows.

- **Brain stem tumours already diffuse on presentation can only benefit from empiric treatment with steroid and radiotherapy. Biopsy is not indicated, Reigel et al 1979, and surgical**

debulking is not an option. Epstein et al, 1986, Stroink et al, 1986, Epstein and Wisoff, 1990, Luh and Roger Bird, 1999

- **Focal midbrain non-cystic gliomas are highly radiosensitive and prognosis is generally good and the five years survival rate is 100% after radiotherapy in all reviewed literature. Albright et al, 1986, Epstein and Wisoff, 1990, Fischbein et al, 1996, Freeman and Farmer, 1998, One of our patients with focal midbrain glioma is alive and symptom-free 12 years following the diagnosis of midbrain glioma and after having been treated by radiotherapy alone and it is possible to talk about cure in this patient. Biopsy is not indicated, Reigel et al 1979, Stroink et al, 1986, Epstein and Wisoff, 1990, and surgical debulking is not an option in focal non-cystic midbrain gliomas. Stroink et al, 1986, Fischbein et al, 1996, Freeman and Farmer, 1998, Luh and Roger Bird, 1999**

- **Focal pontine or medullary non-cystic gliomas, though do benefit from radiotherapy, are best treated by surgical debulking first to be followed by radiotherapy, especially focal tumours that bulge posteriorly (posterior exophytosis). Stroink et al, 1986, Epstein and Wisoff, 1990, Most of the reviewed literatures advocate resection of brain stem gliomas primarily dorsally exophytic into the 4th ventricle. Epstein et al, 1986, Stroink et al, 1986, Tokuriki et al, 1986, Epstein and Wisoff, 1990, Fischbein et al, 1996, Freeman and Farmer, 1998, Luh and Roger Bird, 1999**

- **Cystic focal brain stem gliomas are usually juvenile pilocytic astrocytomas with a large mural nodule and a non-enhancing cyst wall. These tumours are best treated with resection of the neoplastic part of the tumour (mural nodule) and evacuation of the cyst. Epstein and Wisoff, 1990, Prognosis is very good with a 5 years survival rate approaching 89%. Albright et al, 1986, Stroink et al, 1986, Epstein et al, 1986, Tokuriki et al, 1986, Epstein and Wisoff, 1990, Radiotherapy is not indicated after gross total removal of the tumours, Epstein et al, 1986, Epstein and Wisoff, 1990, however some authors recommended administration of antineoplastic agents into the cyst cavity after surgical evacuation. Levin et al, 1984, Ito et al, 1985, It must be noted, however, that cyst wall enhancement is pathognomonic of glioblastomas and surgery is not indicated in such a case. Burger et al, 1985, Burger and Green, 1987, Parisi and Scheithauer, 1993, Fischbein et al, 1996, Freeman and Farmer, 1998, Smirniotopoulos, 1999, Ricci, 1999**

- **Cervicomedullary gliomas are low grade primarily cervical gliomas extending into the lower medulla. These tumours are best treated by surgical debulking to be followed by radiotherapy. Epstein and Wisoff, 1990, The medullary component of the cervical tumour is occasionally a cyst which must be evacuated during surgery. Epstein et al, 1986, Epstein and Wisoff, 1990, Radiotherapy alone was used in this study and although it did stabilize the condition of the patients but it did not improve the preexisting clinical signs. Surgical debulking, on the other hand, can reverse many of the preexisting clinical signs and when associated with postoperative radiotherapy, many patients appeared to have been cured on long term follow up. Epstein et al, 1986, Epstein and Wisoff, 1990, Fischbein et al, 1996, Freeman and Farmer, 1998, Luh and Roger Bird, 1999**

Unfortunately most of the brain stem gliomas are diagnosed when they are in the diffuse rather than focal stage of their natural evolution. Surgery is not indicated in diffuse brain stem gliomas, Epstein et al, 1986, and radiotherapy, though might result in temporary stabilization of the tumours, does not alter the ultimate dismal outcome in diffuse brain stem gliomas. Berger et al, 1983, Fischbein et al, 1996, Freeman and Farmer, 1998, As explained previously all diffuse brain stem gliomas start focally (most probably in the posterior parts of the pons) and delayed diagnosis was the role in all cases. All patients belonging to group (1) gave an initial history of either 6th or 7th nerve palsies, without definite long tract dysfunction, that was misdiagnosed as bells palsy or concomitant squint and most probably the diffuse brain stem gliomas were in the "focal pontine"

stage during those times. The persistent progression of symptomatology and the late appearance of long tracts dysfunction dictated neurological consultation.

The subgroup of patients with focal brain stem low grade gliomas had the best prognosis whether treated by surgical debulking and radiotherapy or radiotherapy alone. Berger et al, 1983, Albright et al, 1986, Epstein et al, 1986, Most of brain stem gliomas are diffuse not because this is the case with brain stem gliomas but because of delayed diagnosis. The prognosis for group (1) patients would indeed be completely different had these patients been diagnosed early enough and during the focal stage of the natural evolution of their disease and it is our view point that early diagnosis was possible in all group (1) patients. Indeed little can be done for a patient presented with a diffuse brain stem glioma. In particular patient number 14 (group 2) lived with an undiagnosed focal posterior pontine glioma for up to 4 years and it was only when the tumour apparently changed its grade, and started disseminating within the brain stem, that this patient came to our attention. Indeed the dismal outcome of this patient would have been changed if he was diagnosed early enough. It is our opinion that picking up cases with diffuse brain stem glioma at an earlier stage is the only practical option, and the only hope, for those patients.

Surgery is not indicated in high grade brain stem gliomas (with short history before clinical presentation and marked clinical disability on presentation). Kaplan et al, 1996, The role of surgery is to reduce as much of the tumour burden as possible. Only patients with focal pontine, focal medullary or cervicomedullary low grade gliomas benefit from surgery that when followed by radiotherapy can result in long term remission and, in fact, it is possible to talk about permanent cure in many of them. Kaplan et al, 1996, Fischbein et al, 1996, Freeman and Farmer, 1998 However brain stem surgery has not been a practical option in Egypt and most neurosurgeons refused to operate on patients with brain stem gliomas and the only patient operated upon in this study (case number 17, group 3) was sent to Germany for operation. However, whenever neurosurgery is not a practical option, radiotherapy alone might be of help. In fact patient number 18 (group 3) with focal pontine glioma dramatically improved by radiotherapy alone as explained earlier in this study.

It must finally be mentioned that three of the four patients belonging to group (2) died immediately following the first session of radiotherapy possibly due to massive tumour necrosis inducing massive brain stem edema and the fourth patient, belonging to group (2), died before radiotherapy. Premedication with steroid is probably indicated before institution of radiotherapy in highly malignant diffuse brain stem gliomas. Chemotherapy was tried in various combination in highly malignant brain stem gliomas with discouraging results. Levin et al, 1984, Jenkins et al, 1987

The single case belonging to group (5) is most interesting. Spinal cord, intramedullary, metastasis was described before, Metwally, 1991. In intramedullary metastasis, the spinal cord is irregular in cross section with asymmetric bulgings and cystic breakdown is not uncommon. However metastasis within the substance of the brain stem is practically, to the best of our knowledge, unheard of. It is of interest to report such a case.

Brain stem gliomas are not a homogeneous group of tumors in so far as the anatomical sites, the clinical picture, the radiological findings, the pathological data, and the prognosis are concerned. Patients in this study were separated into groups with prognostic significance. Grouping the patients in this way was helpful in the general management of those patients. Similar classification was adopted by Epstein and Wisoff, 1990, Luh and Roger Bird, 1999. Data with good and bad prognosis are summarized in table (6). These data are consistent with those reported by Luh and Roger Bird, 1999. Hydrocephalus, when properly shunted, and precontrast CT scan density or MRI signal intensities had no prognostic significance in this study. Hydrocephalus was seen in only 2 patients, 9.5%, belonging to group (3) with focal gliomas.

Table (6) Data of bad and good prognosis in all patients with brain stem glioma

Good prognosis	Bad prognosis
1. Focal tumours 2. Posterior exophytosis 3. Cervicomedullary location 4. The presence of calcification 5. Midbrain location 6. Cystic lesion with non-enhanced wall and a mural nodule 7. Longer history before clinical presentation > 6 months	1. Diffuse brain stem gliomas 2. Patchy, irregular, ringlike contrast enhancement 3. Short history before clinical presentation < 6 months 4. Marked clinical disability on presentation 5. Grade III, VI gliomas 6. Abundance of cranial nerve palsies

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