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Case Series

Childhood brainstem lesions

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ABSTRACT

Brainstem gliomas are more common in the paediatric age group as compared to adults. They have variable clinical presentations, which can range from mild to severe. Radiographic appearance on MRI, anatomical location, and molecular pathology plays a key role in management and prognostication. A multidisciplinary approach based upon the extent and type of tumour is followed. In our study, we have reported 3 such cases who presented in different ways and were diagnosed as brainstem glioma. We have also discussed various modalities of investigation and management.

Keywords: Brainstem gliomas, MRI, Molecular pathology, Multidisciplinary approach

INTRODUCTION

Brainstem gliomas are glial tumors that primarily arise from the brainstem and account for 10-15% of primary CNS tumors in children. The outcome depends upon the tumor location, imaging characteristics, and the patient's clinical status. Patients with these tumors may present with motor weakness, cranial nerve and cerebellar dysfunction, and signs of elevated intracranial pressure. There are mainly 4 types. Dorsally exophytic, cervicomedullary, focal (5-10% each), and diffuse intrinsic pontine glioma (70-85%).

The survival of patients with diffuse pontine glioma is very low compared to that of focal tumors. Surgical resection is the primary treatment approach for focal and dorsally exophytic variants. Cervicomedullary and diffuse intrinsic pontine gliomas are treated by radiation therapy.

Diffuse intrinsic pontine glioma has a unique genetic makeup with mutations in histone H3.3 or H3.1 (80%), with mutations affecting the activin receptor gene (ACVR1). These can present as chronic neurologic deficits, seizure disorders, neurocognitive deficits, and neuroendocrine deficiencies. They also have a significant risk of secondary malignancies, although the prognosis is variable. The WHO system classifies astrocytic tumors into four grades of malignancy, based upon their biological behaviors.

It includes grade I astrocytomas, which are the least aggressive and can be cured with surgery alone, up to grade IV astrocytomas, which are highly aggressive tumors that infiltrate the surrounding brain tissue and are fatal within an average of one year1.About 10% arise in the medulla or cervicomedullary junction. They may be amenable to total or near- total surgical resection and hence carry a favorable prognosis.

In our report, we present three pediatric patients who presented in different ways and were diagnosed with brainstem tumors. The clinical presentation, possible treatment modalities with recent advances, and prognosis were discussed with the backing of a comprehensive literature review.

CASE SERIES

Case 1

A 6-year-old female child, second issue by birth order, born of non-consanguineous parents, had an inability to walk and perform routine activities with drooling of saliva from the right angle of the mouth, weakness over the right half of her body, and repeated episodes of falling with an inability to maintain posture. There was no significant prior history. She was oriented, conscious, and vitally stable.

On examination (both upper and lower extremities), right left (sides of body)

Tone ↑ N Power 3/5 4/5 (all joints)

Deep tendon reflexes were bilaterally brisk, plantar-bilateral upgoing, and the angle of the mouth deviated to the right side with obliteration of the left nasolabial fold, suggesting 7th cranial nerve palsy. Complete blood counts, liver and renal function tests, and coagulation profiles were normal.

Neuroimaging

Computed tomography (CT) scan, bulky mass with ill-defined hypodensity noted in the left cerebral peduncle, midbrain, pons, and cerebellar peduncle. The lesion had a few foci of hyperdensities within it, suggesting of hemorrhages.

This lesion causes a mass effect in the form of compression of the aqueductal sylvius with proximal mildly dilated bilateral lateral and third ventricles noted. Inferiorly, the abovementioned lesion causes compression of the fourth ventricle, suggesting neoplastic space occupying the lesion and the possibility of brainstem glioma.

MRI brain

Heterogeneously enhanced intra-axial lesion of approximate size 7×5.8×4.7 cm seen in the left pons and left brachium pontis, showing a T1 isotense/T2 heterogenous hyperintense signal with blooming on SWI. Diffusion restriction is seen within the tumor, with the lesion extending into the left half of the midbrain. It is expanding with effacement of the posterior fossa cistern, tonsillar herniation (12 mm), and compression on the fourth ventricle. Moderate hydrocephalus of the third and fourth ventricles is seen with minimal periventricular CSF seepage.

The diagnosis was kept as right spastic hemiparesis with ipsilateral seventh cranial nerve upper motor nerve palsy secondary to space-occupying lesion-diffuse brainstem glioma. On the third day of admission, Pat died due to respiratory compromise. A clinical autopsy revealed a diffuse midline glioma with astrocytic differentiation (KH3-K27-Mutant).

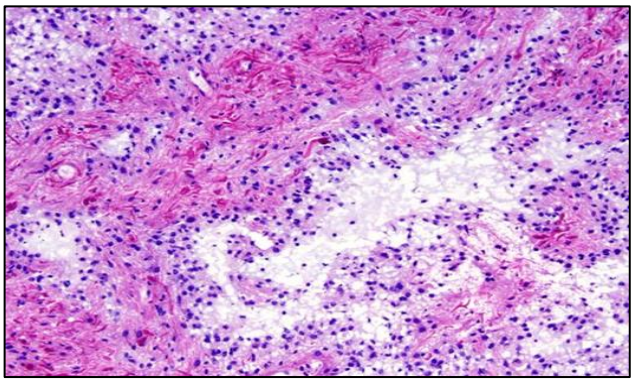

Figure 1: Magnetic resonance image and Histopathological findings.

Case 2

A 10-year-old male child with a complaint of left-sided weakness for 2 months, progressive in nature, and facial weakness since the last 15 days. There was no significant prior history. Vitals were within normal limits. On examination, left-sided power was 2/5 at all joints, and deep tendon reflexes were bilaterally brisk.

Plantars were bilaterally upgoing, the seventh cranial nerve upper-motor-neuron palsy-angle of the mouth deviated to the right, and obliteration of the left nasolabial fold and bilateral forehead wrinkles were preserved.

Complete blood counts, liver and renal function tests, and coagulation profiles were normal.

Neuroimaging

CT scan the brain showed a brainstem enlarged with heterogeneous density with effacement of the posterior fossa and compression of the fourth ventricle, and ill-defined density in the thalamus, suggesting diffuse infiltration of the brainstem glioma.

MRI brain

Heterogeneous enhancement of 5×4.3×5.3 cm in the pons, midbrain, right brachium pontis, right cerebral peduncle, and extending in the right thalamus with compression of the right cistern, right choroidal fissure, and subarachnoid hemorrhage in the pons and midbrain.

Mass effect with compression of the third-fourth ventricle, effacement of the posterior fossa cistern, and tonsillar herniation. MR spectroscopy revealed a raised choline and lactate peak, a reduced N-acetyl aspartate (NAA), and a raised choline, NAA ratio of 5. Mild hydrocephalus of bilateral lateral ventricles. Impression-

diffuse brainstem glioma. The diagnosis was kept as left spastic hemiparesis with ipsilateral seventh cranial nerve upper motor nerve palsy secondary to diffuse brainstem glioma. Neurosurgery advice was taken, a biopsy was advised, and the patient the patient was referred to a higher center for a biopsy of the lesion.

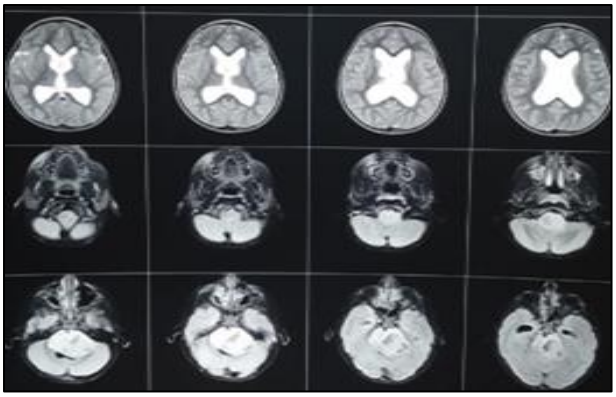

Figure 2: Magnetic resonance image showing brainstem glioma.

Case 3

A 10-year-old male child with complaints of an unprovoked generalized convulsion, one episode a day before admission. General and systemic examinations were normal.

Neuroimaging

A CT scan showed communication hydrocephalus, an ill-defined hypodensity in the caudothalamic region, and generalized oedema.

MRI brain

10×10×13 mm mass in the aqueduct of Sylvius causing moderate hydrocephalus, suggestive of possibly pilocytic astrocytoma or meningioma. Ventriculoperitoneal shunting was done and was referred to a higher center for further investigation and management, as ours is not a cancer treatment centre.

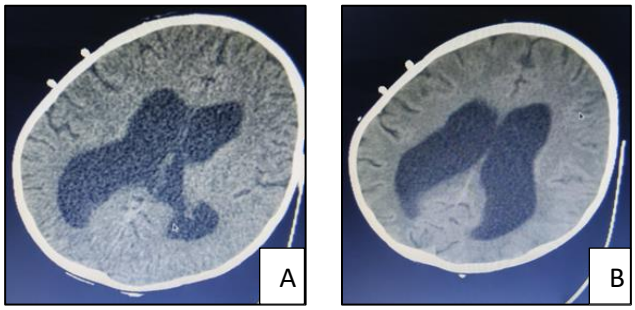

Figure 3 (A and B): CT scan image (Axial).

DISCUSSION

What causes brainstem gliomas? It is still a study subject, but it has been found to have a genetic association. There are a few conditions, like Li-Fraumeni syndrome, neurofibromatosis, and tuberous sclerosis, that have some association. The clinical presentations may vary, so a comprehensive clinical approach is important. Clinical features may include a deviation of the angle of the mouth leading to drooling of saliva, weakness in the limbs, seizures, altered sensorium, postural instability, double vision headaches, and vomiting. In some cases, hydrocephalus can be detected due to compression of the fourth ventricle.[1-3]

Imaging technology like magnetic resonance imaging (MRI) has played a vital role in precisely locating the lesion, showing growth patterns, and determining the feasibility of invasive procedures during diagnosis and interventions. However, we still face problems in the areas of quality diagnosis and robust monitoring of treatment outcomes. For example, it is difficult to use conventional MRI to distinguish WHO grade I pilocytic astrocytoma from WHO grade IV glioblastoma, gliomas from non-gliomas, and neoplastic from non-neoplastic lesions.[4-6] Imaging also fails to detect responses to radiotherapy and chemotherapy and also fails to differentiate between progression or recurrence and radiation-induced necrosis.[7]

The development of molecular pathology has revolutionized diagnostics and helps in diagnosing at the molecular level, which was not possible with neuroimaging techniques. The common mutated genes of children's DIPGs are K27M H3F3A (70%) and ACVR1 (20–30%).[8-10] DIPG patients with K27M-H3F3A mutations have a very poor prognosis. The main mutation in the brainstem pilocytic astrocytoma is the integrated mutation BRAF-KIAA154911, and in the sellar area pilocytic astrocytoma is the mutation V600E BRAF.[12]

Tumors may appear similar and have different molecular genetics, and these genetics may also vary with tumor site. Molecular genetics provides potential targets (ACVR1, IDH1, H3F3A, and BRAF) for drug development. Magnetic resonance perfusion (MRP) imaging is associated with pro-angiogenic genetic expression levels, and magnetic resonance spectroscopy (MRS) can detect carcinogenic 2-hydroxyglutarate products induced by intratumoral IDH1 and 2 genetic modifications.[13,14]

In the Pirotte et al study, PET and CT images were integrated and used in stereotactic biopsy procedures to aim for hypermetabolic foci of intrinsic infiltrative brainstem lesions in 20 children and found that 18 F-FDG and 11C-Methionine (MET) PET could help point out a more accurate diagnostic yield for biopsy to get the tumor tissue for pathological studies. PET imaging improves sampling and reduces the risk of repeated sampling15.

PET/MRI, which combines the benefits of high PET sensitivity with high MRI imaging resolution, will be used more widely in the future.[16] Treatment includes a variety of methods, such as surgery, radiotherapy, chemotherapy, and combination therapy. Surgical treatment is aimed at reducing the major impact of tumor mass and histopathological diagnosis. This method can be used for focal tumors, but for diffuse lesions, radiotherapy is more effective. It can lead to a decrease in neurological symptoms and the elimination of tumor residuals after surgery, which is why it should be started early. Five to ten percent of patients show recurrence at the edges of the radiation fields, suggesting a missed locally aggressive lesion, though whole brain irradiation is not recommended.[18]

The amount of radiation needed to control disease has been extensively studied. Radiation doses >50 GHz are associated with improved survival compared to low radiation doses.[17] Temozolomide, oral etoposide, cyclophosphamide, methotrexate, ifosfamide, carboplatin, cisplatin, topotecan, and alpha-interferon are under trial for their efficacy and are used as an add-on in conditions for diffuse infiltrating brainstem gliomas in which the prognosis is poor. Other symptomatic therapies, such as analgesia, judicious use of steroids for neurological symptoms, and family counseling, are equally important.

CONCLUSION

Supportive multidisciplinary interventions for children with brain tumours both during and after therapy may help improve the ultimate outcome. However, the survival rate depends on the location and extent of the disease. Focal tumours have a better prognosis, whereas diffuse infiltrating tumours are more challenging. Many trials are underway to understand the biologics of tumours and target treatment accordingly. However, in our study, children with variable presentations were diagnosed as having brainstem gliomas and had a guarded prognosis.

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