Case Report

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2024.56.008921

Diffuse Intrinsic Pontine Glioma: Retrospective Case Study of a 19-Year-Old Male at a Kentucky Rural Clinic

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ARTICLE INFO

Received: May 23, 2024

Published: June 05, 2024

Citation: Radwa Clarissa Omar. Diffuse Intrinsic Pontine Glioma: Retrospective Case Study of a 19-Year-Old Male at a Kentucky Rural Clinic. Biomed J Sci & Tech Res 56(5)-2024. BJSTR.MS.ID.008921.

ABSTRACT

Diffuse Intrinsic Pontine Glioma (DIPG) is a proliferative brain tumor that is aggressive in nature and rapid growing. DIPG predominantly affects the pons, a part of the brain stem that is responsible for regulating vital physiologic functions such as breathing, heart rate, and hemodynamic stability. In the United States, about 300 children are diagnosed with DIPG each year, affecting children between 5 and 10 years of age, but may occur in younger populations and in some cases, teenage populations. DIPGs typically have a lethal prognosis due to the inability to surgically resect tumors safely, and current drug and radiation therapies ultimately being ineffective. Survival rates from high-grade brain stem tumors in childhood remain very poor, with one estimate approximating that only four in ten young pediatric patients diagnosed with a DIPG will live one year after diagnosis. This case study exposes a rare case of DIPG in a 19-year-old male at a rural health clinic.

Keywords: Diffuse Intrinsic Pontine Glioma; DIPG; Pediatric Malignancy; Brain Tumor; Glioma; Clinical Trials

Abbreviations: DIPG: Diffuse Intrinsic Pontine Glioma; CVA: Cerebrovascular Accident; TIA: Transient Ischemic Attack; CDK-RB: Cyclin-Dependent-Kinase-Retinoblastoma; CSF: Cerebrospinal Fluid

Introduction

Diffuse Intrinsic Pontine Glioma (DIPG) is a proliferative brain tumor that is aggressive in nature and rapid growing. DIPG predominantly affects the pons, a part of the brain stem that is responsible for regulating vital physiologic functions such as breathing, heart rate, and hemodynamic stability. Additionally, the pons is responsible for the neurological regulation of muscles used for sight, hearing, ambulation, communication, and eating. DIPG is considered a glioma, pointing to its origination from the brain stem's glial cells, which are responsible for supporting and protecting neurons (Childhood diffuse intrinsic pontine glioma, [1]). In the United States, about 300 children are diagnosed with DIPG each year, affecting children between 5 and 10 years of age, but may occur in younger populations and in some cases, teenage populations. DIPG is rarely identified in adult populations. Symptoms of DIPG typically are of a rapid onset and include but are not limited to visual disturbances, difficulty with mastication, dysphagia, unilateral facial paralysis, morning headache, vomiting, extremity weakness, disruption of balance and behavioral changes (Childhood diffuse intrinsic pontine glioma, [1]). Newly diagnosed DIPG is typically treated with external beam radiation and chemotherapy, although many clinicians recommend clinical trials to improve the odds of survival. DIPG is challenging to treat due to its physiologic location, rapidly progressive nature and means by which it alters the histology of healthy tissue. Most children with DIPG do not live longer than 2 years after initial diagnosis (Childhood diffuse intrinsic pontine glioma, [1]).

Case Presentation

History of Present Illness

A 19-year-old white male presents to rural health clinic with a chief complaint of unilateral facial drooping and weakness. He also admits frequent episodes of falling recently with issues concerning his balance. He reports these symptoms have been ongoing for three to four months, but he has not sought out any medical care due to the inability to afford health insurance. He assumed he likely had Bell's Palsy with the facial drooping and the symptoms would resolve spontaneously. Patient denies any visual disturbances. He admits new onset headaches, but states they are manageable. Patient states he has

no issue with ambulation besides the occasional disruption in balance which sometimes causes him to fall. He denies any recent upper respiratory infections, hearing difficulties or shortness of breath.

Social History

Patient denies tobacco, alcohol, or illicit drug use. He is in a monogamous relationship with no children.

Allergies

No known medicine, food, or environmental allergies.

Past Medical History

None.

Past Surgical History

Hernia repair at age 8. Wisdom teeth extraction.

Medications

- Famotidine for heartburn.
- Ibuprofen for headache.

Physical Exam

Vitals: Temperature, 97 F; heart rate 85; respiratory rate, 20; blood pressure 129/83; body mass index, 20.

B well, appearing with left side facial drooping, sitting calmly in a chair, conversing freely, with no apparent motor or sensory defects, in no acute distress, well developed, well nourished.

Head: normocephalic, atraumatic.

Eyes: pupils equal, round, reactive to light and accommodation.

Ears: normal.

Oral Cavity: mucosa moist.

Throat: clear.

Neck/Thyroid: neck supple, full range of motion, no cervical lymphadenopathy.

Skin: no suspicious lesions, warm and dry.

Heart: no murmurs, regular rate, and rhythm, S1, S2 normal.

Lungs: clear to auscultation bilaterally.

Abdomen: normal, bowel sounds present, soft, non-tender, non-distended.

Extremities: no clubbing, cyanosis, or edema.

Neurologic: facial drooping left side.

Initial Evaluation

Laboratory Studies

Initial work-up from primary care clinic revealed low Vitamin D, slight leukocytosis, and subclinical evidence for hyperthyroidism.

CT Head Without Contrast

Impression: Ill-defined mass centered at the left middle cerebellar peduncle and pons with expansion of the pons and edema extending into the left cerebellar hemisphere and left cerebral peduncle. Trace prominence of the ventricular system most notably within the bilateral temporal horns of the lateral ventricles. Early hydrocephalus is suspected.

Differential Diagnosis

- Cerebrovascular Accident (CVA)
- Transient Ischemic Attack (TIA)
- Bell's Palsy
- Acute Otitis Media
- Primary Brain Malignancy
- Subdural Hematoma
- Lyme Disease
- Salivary Gland Tumor
- Guillan-Barre Syndrome (Tiemstra, et al. [2])

Confirmatory Evaluation

MRI of the Brain without contrast confirms expansile pontine mass and associated mass effect. Mild lateral and third ventriculomegaly are also noted. A subtle focus of periosteal new bone formation along the anterior left mandibular ramus is identified, making prior trauma the most likely consideration.

Diagnosis

Based on radiologic findings, a diagnosis of Diffuse Intrinsic Pontine Glioma was made.

Management

A critical step in managing DIPG is obtaining tissue for diagnosis, as this will characterize the lesion for appropriate identification and treatment. Despite the reluctance of past medical practices to biopsy DIPGs due to anatomical location, advancements in technology have birthed stereotactic biopsy, which has been deemed both safe and as diagnostically reliable as the archaic supratentorial biopsy. Additionally, the tissue volume extracted allows for a broad analysis which includes whole-genome sequencing (Bentayebi, et al. [3]). DIPGs typically have a lethal prognosis due to the inability to surgically resect tumors safely, and current drug and radiation therapies ultimately being ineffective. The current standard of care is treatment with oral temozolomide and external radiation therapy for a total of 6 weeks in patients over 3 years of age (Weisbrod, et al. [4]). Some studies have

revealed efficacy of ribociclab therapy in the management of DIPGs, as suspicion exists that the Cyclin-Dependent-Kinase-Retinoblastoma (CDK-RB) pathway is dysregulated in those with DIPG, and a CDK4/6 inhibitor like ribociclab may be useful in lengthening life expectancy (DeWire, et al. [5]).

Discussion

Diffuse Intrinsic Pontine Glioma (DIPG) is an aggressive tumor of the brainstem. It predominantly affects the pediatric population, with approximately 200 to 300 new cases diagnosed every year in the United States. The majority of those affected typically survive less than one year. The primary mode of treatment for DIPG is radiation therapy, as surgical resection can be catastrophic. Radiation is considered a temporary solution and there has been no pharmacologic agent which has been effective in treating DIPGs (Pellot, et al. [6]).

Etiology/Pathophysiology

DIPG formation may be linked to brain development, as many studies suggest that the disease process is mitigated by specific cells that exist in high concentrations, during the initial development of cerebral tissue. This assumption is supported by data showing DIPGs typically occur in childhood during a time when cerebral tissue is active in development, and rarely in adulthood. A notoriously accepted theory for the development of DIPG is a mutation in the H3 gene. On a biological molecular level, the H3K27M gene mutation has been detected in almost 80% of DIPGs. Brainstem tumors affect approximately 300 children in the United States each year and are considered a significant cause of death in pediatric patients diagnosed with neuromalignancies, 80% of which are DIPGs. Pontine gliomas peak around 6-9 years of age and appear to prefer the male gender and comprise 20% of all childhood tumors (Pellot, et al. [6]).

Diagnosis

DIPGs frequently present with three very common symptoms including ataxia, pyramidal tract dysfunction, and an abducens nerve, or facial palsy. Facial palsy is present in most patients at diagnosis and is typically the initial sign of DIPG. DIPGs often present acutely and the best diagnostic study to evaluate any suspicion of a glial tumor is an MRI of the brain with and without contrast. An expanded pons and basilar artery encasement are usually seen on imaging and a T2 FLAIR shows signal in more than half of the ventral pons. The epicenter of the DIPG is usually within the pons, however it is not uncommon to see regional dissemination into the cerebellum at diagnosis. It is common for glial tumors to spread throughout the central nervous system including the medulla, lateral ventricles, midbrain, cerebellum, thalamus, hippocampus, and frontal lobe. Lumbar puncture is becoming more of a reasonable option, given the metastatic nature of DIPG, as Cerebrospinal Fluid (CSF) may be used to evaluate the molecular characteristics of glial tumors (Vitanza, et al. [7]).

Treatment

Oral corticosteroids are the most prescribed initial treatment for newly diagnosed DIPG. A minority of the affected populous require emergent radiotherapy and treatment for hydrocephalus, typically due to the rapid onset of biological disease. A stereotactic needle biopsy may be considered if molecular findings are required for a specific clinical trial. Pontine biopsies have been shown to be clinically safe at experienced healthcare facilities, and while neurological adverse events are rare, they can be severe and are a potential risk. Radiotherapy should be initiated regardless of whether a biopsy has been performed or not. Oral corticosteroids are used to alleviate symptoms in the interim between biopsy and initiation of radiation (Vitanza, et al. [7]).

Prognosis

Survival rates from high-grade brain stem tumors in childhood remain very poor, with one estimate approximating that only four in ten young pediatric patients diagnosed with a DIPG will live one year after diagnosis. The studies conducted thus far fail to clearly demonstrate symptom improvement over time or render any major impact of chemotherapy or radiotherapy approaches (Hassan, et al. [8]). The outcome of DIPG is extremely poor and equivalently fatal, however there are a sub-group of patients who experience longer survival times. There appears to be 3 favorable prognostic factors which include age at the time of diagnosis being 3 years or less, longer periods of time between symptom onset and diagnosis and the absence of cranial nerve palsy at time of presentation (Vanan, et al. [9]).

Conclusion

Patients with Diffuse Intrinsic Pontine Gliomas (DIPG) have a historically poor prognosis. Although DIPG constitute roughly 10 percent of all pediatric neuromalignancies, they are a primary cause of death in this group. Despite a plethora of clinical trials in newly diagnosed DIPG over the past decade, there has been no evident improvement in prognosis. However, knowledge concerning the physiology of DIPG is increasing, due in part to the introduction of biopsies and autopsies, gene expression profiling, and construction of in vivo models. No clear improvement in survival has been achieved in recent years (Jansen, et al. [10]). In the case of the 19-year-old male reported in this case study, time of survival was approximately 4 months.

Conflict of Interest Statement

The author declares that there is no conflict of interest.

Ethic Statement

This article does not contain any studies involving human participants performed by the author.

Funding

The author received no financial support for the research, authorship, or publication of this article.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2024.56.008921

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Submission Link: https://biomedres.us/submit-manuscript.php