Original Article

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Stereotactic Brainstem Biopsy in Children: A Multicentric Case Series of 88 Patients

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Introduction: Brainstem tumors pose a significant challenge in pediatric neurosurgery. Although MRI has advanced non-invasive diagnostics, up to 20% of cases show radiologic-histologic discordance, making stereotactic biopsy an important diagnostic option. This study aimed to assess the safety, diagnostic effectiveness, and clinical significance of stereotactic brainstem biopsy in a large pediatric cohort.
Methods: We conducted a multicentric retrospective review of 88 children with intrinsic, non-resectable brainstem lesions who underwent stereotactic biopsy (frame-based or robot-assisted). Demographic data, surgical technique, histopathological diagnosis, and complications were analyzed.
Results: Eighty-eight pediatric patients (median age 7 years, range 1.5–17; 54% male) underwent stereotactic brainstem biopsy. The most common presenting symptom was cranial nerve dysfunction, with the pons affected in 76% of cases. Stereotactic frame-based, robot-assisted, and Talairach techniques were used in 10%, 31%, and 59% of cases, respectively. The initial diagnostic yield was 97.7%. The most common diagnoses were high-grade glioma, including diffuse midline glioma (44%), followed by low-grade glioma (41%). The overall complication rate was 9.2%, primarily transient neurological deficits. No procedure-related deaths occurred. The mean follow-up period was 32 months.
Conclusion: Stereotactic brainstem biopsy is a safe and effective diagnostic tool in children, offering high diagnostic yield with low morbidity. Continued advances in technique and molecular analysis further enhance its clinical value.

Keywords: Brainstem Tumor, Stereotactic Biopsy, Robot, Children, Case series

INTRODUCTION

Brainstem tumors (BST) in children pose a significant clinical challenge due to their critical anatomical location and the variety of underlying pathologies [1,2]. Although advances in neuroimaging, especially magnetic resonance imaging (MRI), have enhanced the non-invasive diagnostic approach, MRI alone may not be sufficient for definitive diagnosis in several cases. Up to 20% of pediatric BST show discrepancies between radiologic and histological findings, highlighting the important role of tissue confirmation for accurate classification and treatment planning [3-9]. Histopathological analysis remains the gold standard for diagnostic accuracy, prognostic evaluation, and the increasing need for molecular characterization, particularly for entities such as diffuse midline glioma and diffuse intrinsic pontine glioma, which have unique biological profiles and clinical implications [7,10-12].

The main reason for a brainstem biopsy is to get a precise tissue diagnosis, especially when neuroimaging results are unclear or there is an unusual clinical presentation [7]. Histopathological confirmation directly affects prognosis and allows for personalized treatment, including eligibility for targeted therapies and clinical trials. Stereotactic BST biopsy is a minimally invasive and highly accurate method for sampling brainstem lesions, with studies showing diagnostic yields over 90% and low complication rates and mortality [1-28].

This multicenter study aims to evaluate the diagnostic accuracy, complication profile, and clinical impact of stereotactic brainstem biopsy in a large pediatric cohort, with particular emphasis on the pathological spectrum and procedural safety.

MATERIALS AND METHODS

This is a retrospective study of children who underwent stereotactic biopsy of brainstem lesions at Infantil Hospital of Nossa Senhora da Gloria (HINSG) in Vitória, Brazil, from 2018 to 2023, and at Hôpital Roger Salengro (HRS) in Lille, France, between 1988 and 2017. Inclusion criteria included patients under 18 years old with intrinsic, non-resectable

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brainstem lesions of unknown origin that required biopsy based on a multidisciplinary neuro-oncology board discussion. Brainstem lesions were identified on prior diagnostic cerebral MRI as involving the mesencephalon (tectum or tegmentum), pons, or medulla oblongata. Lesions in the middle cerebellar peduncle extending into the cerebellum, those in the diencephalon, or diagnosed as diffuse pontine glioma on MRI were excluded. Patient demographic data, clinical presentation, biopsy technique and approach, complications, and final histopathological diagnosis were collected and analyzed. This study follows the Consensus Preferred Reporting of Case Series in Surgery guidelines (PROCESS 2023) [29].

All procedures were performed under general anesthesia using either a frame-based or frameless stereotactic system. The approach was chosen based on lesion location and the surgeon's preference. The target was identified according to gadolinium enhancement, tumor borders, and nearby functional structures. Three different techniques for targeted assessment were used: 1) Frame-based with the TB-09 Micromar stereotactic frame (Micromar, São Paulo, Brazil); target coordinates were determined using preoperative MRI combined with CT scans through stereotactic planning software (MNPS, Mevis, São Paulo, Brazil), along with the Shaltenbrand and Wahren Atlas. Tissue samples were processed for intraoperative frozen smear analysis by the pathologist, minimizing tissue collection. 2) Frame-based using the Talairach frame with ventriculography or angiography. The Sedan-Vallicciono side-cut needle was advanced to the planned target, and specimens were taken in a circular pattern at different depths without intraoperative pathological examination. 3) The Neuromate robot (Renishaw, Gloucestershire, UK) was used for frameless stereotactic biopsy, utilizing preoperative 3D T1- and T2-weighted brain MRIs and the robot software VoXim for surgical planning [3,9,13,26]. A passive robotic arm was used during the biopsy. The sample was obtained following the same method as with the Talairach frame. The procedure was deemed successful if the specimens provided a diagnosis based on histology, immunohistochemistry, and/or molecular markers.

Approval from the Health Science Center Ethics Committee at the Federal University of Espírito Santo (90668625.9.0000.5060) and the French College of Neurosurgery (n° IRB00011687) was obtained.

RESULTS

A total of 88 pediatric patients underwent stereotactic brainstem biopsy across two centers (10 at the HINSG and 78 at the HRS), with a median age of approximately 7 years (range 1.5–17 years), and a slight predominance of males (54%). The duration of symptoms ranged from 0.25 to 48 months, with an average of 9.6 months before diagnosis. The most common symptom was cranial nerve dysfunction, mainly oculomotor disturbance, followed by ataxia, hemiparesis, and intracranial hypertension. The most common location was the pontine region, present in 76.1% of patients. Most procedures used a stereotactic frame-based system (86%), while 14% were robot-assisted. The transfrontal a`pproach was employed in 82 cases (93.2%), and the transcerebellar approach in 6 cases (6.8%). An initial diagnosis was achieved in 86 children (97.7%).

The most common histopathological diagnosis was high-grade glioma (Figure 1a), including diffuse midline glioma, diagnosed in 39 cases (44%). Low-grade glioma (Figure 1b) was identified in 36 patients (41%). Pilocytic astrocytoma (Figure 1c) accounted for 4 cases (5%), while ganglioglioma and primitive neuroectodermal tumor (PNET) were each found in 2 patients (2%). Ependymoma, multiple sclerosis (Figure 1d), and inflammatory (rhombencephalitis) lesions were each present in 1 patient (1%), and gliosis was diagnosed in 2 cases (2%). One case initially diagnosed as gliosis was re-biopsied, and the final diagnosis after the second procedure was low-grade glioma. Cases operated on after the 2016 WHO Classification of Tumors of the Central Nervous System [30], as well as others based on previously collected samples, had genetic analysis for histone mutations performed in 13 cases, revealing 8 cases of diffuse midline glioma with an H3.3 (K27M or K28M) mutation.

The overall complication rate was low at 9.2%, mainly involving transient neurological deficits (7%), such as temporary cranial nerve palsy and mild hemiparesis, both of which resolved within a few weeks. There was one case (1.1%) of wound infection that required antibiotics. A persistent lower cranial nerve palsy occurred in one case (1.1%). There were no procedure-related deaths. The follow-up period ranged from 4 days to 246 months, with a mean of 32 months.

DISCUSSION

Our study confirms previous findings that stereotactic biopsy in pediatric brainstem lesions is both feasible and safe, with diagnostic yields reported between 80% and 100% and complication rates ranging from 5% to 15% [1-6,11,13,20,26]. The current data support these results, showing similarly high diagnostic accuracy and an acceptable rate of complications. Recent advancements, including the adoption of frameless stereotactic and robot-assisted techniques, have further improved procedural safety and effectiveness [5,11,26,13].

The main reason for a brainstem biopsy is the need for a definitive histopathological diagnosis, which is essential for optimal patient management. Several studies have shown a significant discrepancy between preoperative radiological impressions and definitive pathological results, with up to 20% of cases displaying radiologic–histologic mismatch [3,4,6,17,26]. Biopsy is especially valuable for distinguishing neoplastic from non-neoplastic lesions, such as

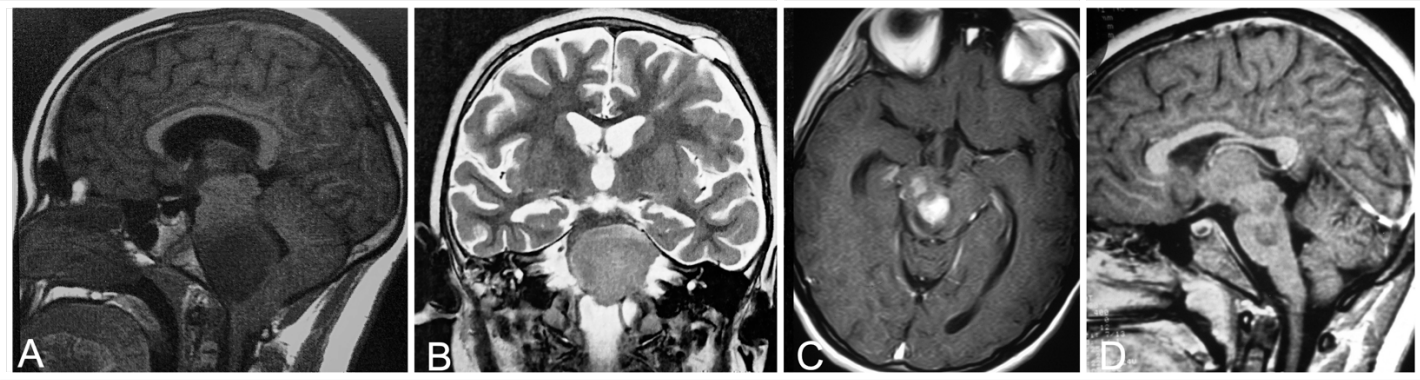

Figure 1. Magnetic resonance imaging of brainstem lesions. (A) Sagittal T1-weighted sequence showing a high-grade glioma; (B) Coronal T2-weighted sequence demonstrating a low-grade glioma; (C) Axial T1-weighted sequence revealing a pilocytic astrocytoma; (D) Sagittal T1-weighted sequence of a demyelinating lesion consistent with multiple sclerosis.

inflammatory or infectious causes that may resemble tumors on imaging. The development of molecular neuro-oncology has highlighted the importance of tissue sampling, as key molecular alterations—such as the H3K27M mutation in diffuse midline gliomas—have significant diagnostic, prognostic, and therapeutic implications [7,8,10,28,30]. In cases suspected of high-grade glioma, biopsy not only confirms the histological grade but also provides vital molecular data that may guide targeted treatments [8,10,28]. For example, identifying actionable genetic mutations now influences eligibility for clinical trials and access to experimental therapies, emphasizing the importance of tissue diagnosis [7,28,30]. Stereotactic biopsy, whether frame-based, frameless, or robot-assisted, remains the most common and reliable method for obtaining diagnostic tissue from deep-seated brainstem lesions [11,13,20,26]. Frameless stereotactic systems, which incorporate advanced image guidance and real-time navigation, offer greater flexibility during procedures and shorter operation times [11,26]. Careful planning of the trajectory—aimed at avoiding critical structures like the corticospinal tract and cranial nerve nuclei—is crucial to reduce morbidity [26,27]. Typically, multiple tissue samples are taken from different areas within the lesion to maximize diagnostic success and account for tumor heterogeneity. The present series achieved a diagnostic yield of 97.1%, consistent with previously reported rates of 86%–100% in pediatric populations [3,4,6,21,26]. Notably, a large meta-analysis including 735 children reported a diagnostic yield of 96.1%, with an overall morbidity rate of 6.7%, permanent morbidity of 0.6%, and mortality of 0.6% [5]. These results support the safety and effectiveness of stereotactic biopsy for pediatric brainstem lesions, including transcerebellar approaches, which may be chosen based on the location without significantly increasing the risk of complications [20,26,27]. The tissue obtained is usually sufficient for histopathological and molecular studies, enabling both diagnosis and comprehensive molecular profiling. This not only ensures accurate diagnosis but also helps determine patient eligibility for next-generation clinical trials involving targeted therapies [28,30].

Limitations of our study include its retrospective nature and variability in patient characteristics, such as lesion type, location, and size. Nevertheless, the data strongly support the role of stereotactic brainstem biopsy in the current management of pediatric brainstem lesions. Future research should aim to identify predictors of diagnostic success and complications, as well as evaluate the impact of biopsy-guided treatment on long-term outcomes and quality of life [5,27].

CONCLUSION

Stereotactic brainstem biopsy is a highly effective and safe procedure in the pediatric population, providing a high diagnostic yield with low morbidity. It plays a crucial role in establishing definitive diagnoses and guiding the management of intrinsic brainstem lesions in children. Ongoing advancements in stereotactic techniques, neuroimaging, and molecular diagnostics continue to improve both the safety and clinical value of this method. Future research should focus on identifying predictors of diagnostic success and complication risk, as well as clarifying the long-term effects of brainstem biopsies on clinical outcomes and quality of life in pediatric patients.

DISCLOSURES

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local Ethics Committee, number: Health Science Center

Ethics Committee at the Federal University of Espírito Santo (90668625.9.0000.5060) and the French College of Neurosurgery (n° IRB00011687)

Consent to participate

The patients gave consent to use their information and images for research purposes. *Consent for publication*

Conflict of interest

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Artificial intelligence

No artificial intelligence assistance were employed in the preparation of this manuscript.

CONTRIBUTIONS

-**Walter Fagundes**: Conceptualization, Data curation, Formal Analysis, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing
-**Sergio Dantas**: Visualization, Data curation, Writing – review & editing
-**Nicolas Reyns**: Visualization, Writing – original draft, Writing – review & editing
-Gustavo Touzet: Visualization, Writing – original draft, Writing – review & editing **-François Dubois**: Data curation, Investigation
-Serge Blond: Visualization, Writing – original draft, Writing – review & editing, Supervision

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