

## Brainstem gliomas ... the devil is in the details

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See the article by Patil et al. in this issue, pp. 990–998.

Brainstem high-grade gliomas (HGG) account for approximately 10–15% of childhood CNS tumors.<sup>1</sup> However, due to their invasion to eloquent structures, histological confirmation has been routinely avoided, and clinical and radiological characteristics have been used for diagnosis. Recent molecular studies unveiled a significant biological heterogeneity among them and demonstrated the prognostic significance of different driver mutations in this population<sup>2</sup> thus, explaining the prolonged survival reported in of some patients<sup>3</sup> in an otherwise lethal disease.

In this issue of *Neuro-Oncology*, Patil et al.<sup>4</sup> provide an overview of the epidemiological landscape of children and adolescents diagnosed with brainstem gliomas in the United States using a large population-based cohort assembled using the Central Brain Tumor Registry of the United States (CBTRUS) and NCI Surveillance, Epidemiology and End Results (SEER) cancer registry over a 17-year period.

In a laudable effort, the authors provide comprehensive epidemiological characterization powered by the large number of patients. A total of 4486 patients were included in this study, making it the largest cohort of children and adolescents with brainstem gliomas to date. The overall age-adjusted incidence rate (AAIR) was estimated to be 0.305 per 100 000 population and identified a higher incidence in white children (0.23) and children between the ages of 0–4 and 5–9 years (0.38 and 0.5 × 100 000, respectively). The incidence rates are equivalent to smaller cohorts previously reported in the United States<sup>5</sup> although it compares slightly higher than a recent report from the Canadian Pediatric Brain Tumor Consortium (CPBTC) that only included patients with diffuse intrinsic pontine glioma (DIPG) after careful central radiological review. Suggesting the inclusion of non-DIPG in the present study may account for the slightly higher incidence rate.<sup>6</sup>

This study highlights the historical scarcity of biological samples in brainstem gliomas and its contribution to our poor understanding of the molecular underpinnings and the paucity of accurate epidemiological estimates of this entity. In this study, 70% of the study population lacked histological confirmation,<sup>4</sup> leading to the inevitable inclusion of other pathologies

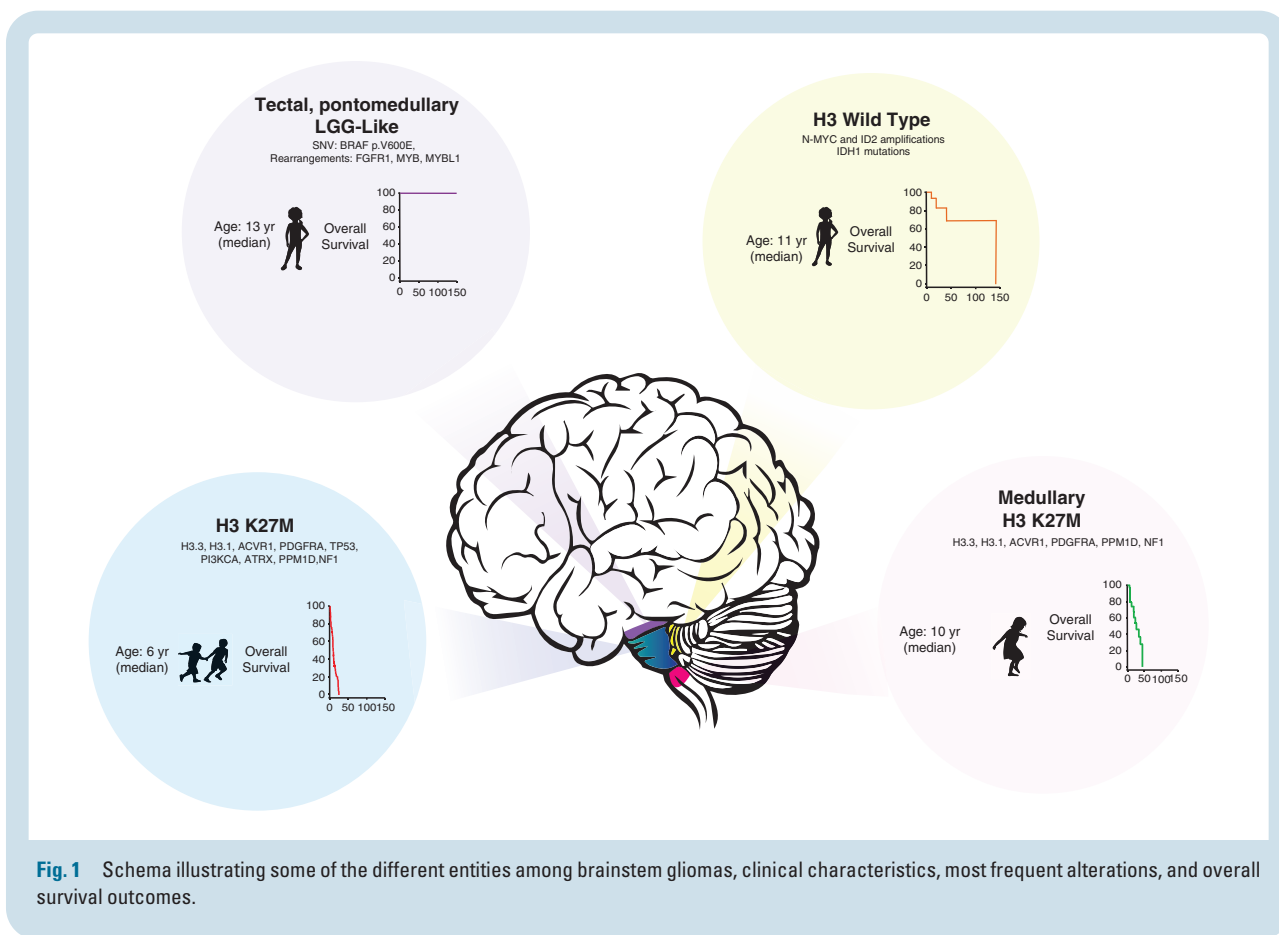
and therefore encumbering the interpretation of the results. Furthermore, this study provides an impetus to establish stereotactic biopsies and tissue diagnosis as the standard of care for proper classification and treatment of brainstem gliomas.

Accounting for 80% of childhood brainstem tumors, malignant midline gliomas frequently harbor hotspot point mutations in the histone variants H3.1 and H3.3<sup>2</sup> and remain a disheartening fatal diagnosis. Recent studies demonstrated that brainstem gliomas encompass different entities with distinct oncogenic mechanisms, clinical characteristics, and disparate outcomes.<sup>7</sup> Due to the inability to account for the biological heterogeneity of brainstem HGG in the present study, the survival outcomes may seem overestimated and require careful interpretation.

Another important confounder of this population-based analysis is the need to rely on the International Classification of Diseases for Oncology, third edition (ICD-O-3) coding, to identify the study subjects. In combination with the absence of histological confirmation, the probable inclusion of low-grade gliomas located in the brainstem may explain the unexpectedly high survival of the entire cohort and particularly in the subgroup of patients diagnosed by radiological criteria. In contrast, the survival of patients with histologically proven HGG is akin to the results as previously described in other registry studies<sup>3</sup> and prospective clinical trials.<sup>8</sup> Thus, the survival presented illustrates the summation of wide spectrum of diseases as depicted in [Figure 1](#).

Notably, the identification of age as a prognostic factor is presumably a surrogate for biology as the majority of patients with histone mutated tumors present between 1–9 years of age. Furthermore, the superb survival reported in children younger than 1 year could represent the outcome of low-grade gliomas in which higher mitotic figures are frequently observed and often histologically “upgraded”<sup>9</sup> or the unique biological behavior of infantile gliomas.<sup>10</sup>

The true epidemiology of brainstem gliomas remains to be elucidated and will require the centralized selection of cases and the incorporation of biological markers for accurate estimation. Disease-specific registries such as the International Diffuse



**Fig. 1** Schema illustrating some of the different entities among brainstem gliomas, clinical characteristics, most frequent alterations, and overall survival outcomes.

Intrinsic Glioma Registry (IDPGR) (<https://dipgregistry.org/>) and the European Society for Pediatric Oncology (SIOPE) DIPG network registry (<https://www.dipgregistry.eu/>) have modeled the acquisition and curation of clinical, radiological, and biological data, and aim to improving the veracity of the information collected and providing reliable estimations. Notwithstanding, the retrospective nature of these registries has its own set of limitations.

Patil et al.<sup>4</sup> lay a foundation with this remarkable study and highlight the overwhelming importance of incorporating biological data into population-based dataset for proper disease characterization as we evolve into a molecularly driven classification of maladies.

## Keywords

brainstem gliomas | DIPG | epidemiology | high-grade glioma

## Funding

AF is supported by the WE LOVE YOU CONNIE FOUNDATION.

## Acknowledgments

The text is the sole product of the authors and no third party had input or gave support to its writing.

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