Infant-Type Hemispheric Gliomas: A Review of Clinical, Radiologic, Histopathologic, and Molecular Features

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Abstract

Infant-type hemispheric gliomas (IHGs) are extremely rare, large, hemorrhagic tumors of the cerebral hemispheres commonly diagnosed during infancy. Treatment of IHG has been adapted from historical clinical trials that enrolled infants with high-grade glioma (HGG) and involves maximal safe surgical resection followed by adjuvant chemotherapy. With this treatment, IHGs have shown good overall survival rates in retrospective studies; however, survivors have poor long-term neurologic and neurocognitive outcomes because the clinical course is fraught with high rates of surgical morbidity, acute intracranial hemorrhage, tumor progression, and use of multiple chemotherapy regimen for treatment. At the molecular level, IHGs are uniquely driven by RTK fusions, and their DNA methylation profiles distinguish them from other pediatric-type diffuse HGGs while clustering more closely with low-grade desmoplastic infantile ganglioglioma/astrocytoma. Although RTK fusions render IHGs targetable by tyrosine kinase inhibitors (TKIs), their optimal role in infants is yet to be determined. Consequently, TKIs are most often used in the recurrent setting, while surgery and chemotherapy continue to represent the standard primary treatment approach. This review summarizes historical clinical trials, delineates the histopathologic and molecular landscape of IHG, and highlights current therapeutic gaps, underscoring the need for collaborative research efforts to establish standardized treatment approaches.

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Infant-type hemispheric glioma (IHG) is a newly recognized brain tumor entity in the 5th edition of the *WHO Classification of Tumors of the Central Nervous System* (CNS) published in 2021. Commonly diagnosed during infancy, these large hemorrhagic tumors can encompass an entire cerebral hemisphere. Their genomes often harbor oncogenic structural rearrangements of RTK (*NTRK1/2/3*, *ALK*, *ROS1*, and *MET*). Epigenetically, IHGs have a distinct methylation profile from other classes of pediatric-type diffuse high-grade gliomas (pHGGs).[1]

Conventional management of maximal surgical resection followed by involved-field radiation therapy (RT) was a standard approach for all children with high-grade gliomas (HGGs). However, RT to the developing nervous system of very young children (generally <3 years of age) can cause unacceptable rates of toxicities, including growth failure, severe cognitive impairment, and leukoencephalopathy. Therefore, early clinical trials enrolling infants and young children with HGG focused on delaying or avoiding radiation with multiagent adjuvant chemotherapy after maximal safe surgical resection.[2–8] Anecdotally, despite the omission and/or delay of RT, infants were observed to have better survival than older children and adolescents with HGG,[2–8] suggesting that underlying biological differences in tumors of the younger population are a probable cause. Despite the better prognosis, >50% of infants with HGG experienced disease progression during or after primary treatment and often required multiple secondary surgeries and different chemotherapies as second- or even third-line treatment, leading to a high rate of therapy-associated morbidity among survivors.[6,9] Most importantly, biologic predictors of clinical outcomes were unknown, making it difficult to anticipate prognosis in an individual infant with HGG. This critical knowledge gap prompted collaborative multi-institutional and multinational investigations into the epigenomic, genomic, and transcriptomic aberrations of pHGG, which have revolutionized our understanding of gliomas diagnosed during infancy and ultimately led to the recognition of IHG as a novel diagnostic entity.

Historical Trials in Young Children

Table 1 summarizes historical clinical trials enrolling infants with HGG. One of the first trials to enroll infants with HGG was Pediatric Oncology Group 1 (POG1), in which children aged <36 months received postoperatively systemic chemotherapy followed by RT. The study enrolled 32 infants with glioma diagnosis (brainstem glioma, n=14; malignant glioma, including anaplastic astrocytoma [AA] and glioblastoma multiforme [GBM], n=18). The 2-year mean progression-free survival (PFS) rate was 28% (SE, 16.7%) for patients with brainstem glioma and 54% (SE, 18.3%) for those with malignant glioma. The corresponding 2-year mean overall survival (OS) rates were 42% (SE, 14.2%) and 65% (SE, 12.8%), respectively.[2] Similarly, 39 infants aged <24 months diagnosed with malignant astrocytoma (AA, n=20; GBM, n=8; anaplastic mixed glioma, n=3; and gliosarcoma, n=1) were treated with 10 courses of chemotherapy followed by RT on a Children's Cancer Group (CCG) protocol. The study reported 3-year PFS and OS rates of 36% and 51%, respectively, and only 4 patients received RT on the protocol.[4] A trial of high-dose chemotherapy (HDC)–autologous bone marrow reconstitution (ABMR) enrolled 15 patients aged <72 months (malignant glioma, n=9; brainstem

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Table 1. Selected Clinical Trials of HGG in Infants and Young Children and Reported Outcomes

Study	Treatment	Diagnosis	Survival
POG1[2] 1986–1990 Newly diagnosed brain tumor Age <36 mo	**Radiation-delaying strategy** Cycle A: CPM + VCR Cycle B: CDDP + VP16 Repeated courses of A and B cycles from diagnosis until age 3 years and then RT offered	Brainstem glioma: n=14 Malignant glioma: n=18 (AA & GBM) Total: N=32	**Brainstem glioma** • 2-y PFS: 28% (SE, 16.7%) • 2-y OS: 42% (SE, 14.2%) **Malignant glioma** • 2-y PFS: 54% (SE, 18.3%) • 2-y OS: 65% (SE, 12.8%)
CCG 945[4] 1985–1991 Newly diagnosed malignant astrocytoma Age <24 mo	**Radiation-delaying strategy** Chemotherapy (8 drugs in 1 day) VCR + BCNU + HU + CDDP + ARA-C + Pred + DTIC 10 courses and then RT	AA: n=20 GBM: n=8 AMG: n=3 GS: n=1 Total: N=32	**Entire cohort** • 3-y PFS: 36% (SE, 8%) • 3-y OS: 51% (SE, 8%)
Head-Start I[7] 1991–1995 Newly diagnosed Age <72 mo	**Radiation-sparing strategy** HDC-AuSCR Induction: CDDP, CPM, VP16, VCR Consolidation: HDC: Thiotepa, VP16, Carbo, and AuSCR 5 cycles chemotherapy followed by AuSCR after maximal surgical resection RT optional if residual tumor present	Malignant glioma: n=9 Brainstem glioma: n=6 Total: N=15	**Entire cohort** • 2-y EFS from diagnosis: 27% (95% CI, 15%–39%) • 2-y OS from diagnosis: 48% (95% CI, 36%–60%) **Malignant glioma** • 2-y EFS from diagnosis: 11% (95% CI, 0%–32%) • 2-y OS from diagnosis: 22% (95% CI, 0%–50%) **Brainstem glioma** • 2-y EFS from diagnosis: 17% (95% CI, 0%–47%) • 2-y OS from diagnosis: 33% (95% CI, 0%–41%)
BBSFOP[5] Age <60 mo	**Radiation-delaying strategy** Chemotherapy Carbo/PCB CDDP/VP16 VCR/CPM 7 cycles of 3 drug pairs over 16 months with RT in case of recurrence/progression	AO: n=4 O: n=4 GBM: n=5 OA: n=1 A: n=7 Total: N=21	**Entire cohort** • 5-y PFS: 35.3% (95% CI, 16%–52%) • 5-y OS: 58.8% (95% CI, 34%–73%) **Malignant glioma** • 2-y PFS: 45.4% (95% CI, 16%–52%) • 2-y OS: 65% (95% CI, 34%–73%)
UKCCSG/SIOP CNS 9204[8] 1993–2003 Age <36 mo	**Radiation-delaying strategy** Chemotherapy Carbo, VCR, MTX, CPM, CDDP Seven 56-day cycles, started within 4 weeks of surgery and continued for 1 year, radiation withheld unless progressive disease	A: n=26 HGG (not midline): n=18 DIPG: n=7	**A** • 5-y EFS: 13.2% (95% CI, 3.4%–29.6%) **HGG** • 5-y EFS: 18.1% (95% CI, 4.6%–38.6%) • 5-y OS: 34.7% (95% CI, 14.6%–56.0%) **DIPG** • 1-y EFS: 0.0% • 3-y OS: 0.0%
SJYC07[6] 2007–2017 Published analysis included 15 patients treated on institutional protocol and 41 patients were enrolled on SJYC07 trial Patients with histologic diagnosis of HGG Age <36 mo	**Radiation-sparing strategy** HD-MTX, CDDP, CPM, VCR, Carbo, VP16, Topo	AA: n=11 APA: n=1 GBM: n=10 HGG: n=9 HGNET: n=9 PG: n=1 Total: N=41	**Entire cohort** • 5-y EFS: 51.06% (95% CI, 37.99%–69.05%) • 5-y OS: 78.05% (95% CI, 66.35%–91.80%)

Abbreviations: A, astrocytoma; AA, anaplastic astrocytoma; AMG, anaplastic mixed glioma; AO, anaplastic oligodendroglioma; APA, anaplastic pilocytic astrocytoma; ARA-C, cytarabine; AuSCR, autologous stem cell rescue; BCNU, carmustine; Carbo, carboplatin; CDDP, cisplatin; CPM, cyclophosphamide; DIPG, diffuse intrinsic pontine glioma; DTIC, dacarbazine; EFS, event-free survival; GBM glioblastoma; GS, gliosarcoma; HD-MTX, high-dose methotrexate; HDC-AuSCR, high-dose chemotherapy with autologous stem cell rescue; HGG, high-grade glioma; HGNET, high-grade neuroepithelial tumor; HU, hydroxyurea; O, oligodendroglioma; OA, oligoastrocytoma; OS, overall survival; PCB, procarbazine; PFS, progression-free survival; PG, pilomyxoid glioma; Pred, prednisone; RT, radiation therapy; Topo, topotecan; VCR, vincristine; VP16, etoposide.

glioma, n=6), who received adjuvant chemotherapy consisting of myeloablative doses requiring stem cell rescue following surgery.[7] The study reported 2-year event-free survival (EFS) and OS rates of 27% and 48%, respectively. The BBSFOP trial enrolled 21 infants with glioma aged <5 years at diagnosis (anaplastic oligodendroglioma [AO], n=4; oligodendroglioma, n=4; GBM, n=5;

astrocytoma, n=7; and oligoastrocytoma, n=1). Patients received 7 courses of postoperative adjuvant chemotherapy, with RT reserved only for cases of relapse or disease progression. The trial reported 5-year PFS and OS rates of 35.3% and 58.8%, respectively; 6 infants received RT on trial.[5] A total of 26 infants (age <3 years) diagnosed with astrocytoma (nonmidline HGG, n=19; diffuse intrinsic pontine glioma, n=7) were treated in the Children's Cancer and Leukemia Group (UKCCSG) trial over a 10-year period (1993–2003). Those with nonmidline HGG had 5-year EFS and OS rates of 18% and 34.7%, respectively. Radiation was used only as a salvage treatment in the event of progression or relapse.[8] A total of 41 patients aged <36 months diagnosed with HGG were enrolled in the multicenter St. Jude Young Children 07 (SJTC07) trial between 2007 and 2017. Diagnoses included AA (n=11), anaplastic pilocytic astrocytoma (n=1), glioblastoma (n=10), HGG (n=9), high-grade neuroepithelial tumor (HGNET; n=9), and pilomyxoid glioma (n=1). Following surgical resection, patients received adjuvant chemotherapy based on high-dose methotrexate. The trial reported EFS and PFS rates of 46.73% and 76.16%, respectively, with only 2 patients receiving RT after relapse.[6]

These earlier trials reported a better survival rate in infants diagnosed with HGG, often achieved without the use of RT. Although this alternative clinical behavior has suggested a potentially different molecular pathogenesis in infantile HGG, features differentiating infantile HGG from those occurring in older children remain to be elucidated.

Molecular Characteristics and Evolution of IHG

In 2014, Wu et al[10] reported gene fusions involving *NTRK1*, *NTRK2*, and *NTRK3* in non-brainstem pediatric HGGs, based on a comprehensive genomic analysis of 127 tumors. In 2019, Guerreiro Stucklin et al[11] published a largescale multi-institutional molecular study of 118 gliomas diagnosed in patients aged ≤12 months. Tiered molecular profiling of single nucleotide variants, structural variants, and copy number alterations identified a distinct group of HGGs in the cerebral hemispheres, characterized by gene fusions in *ALK*, *ROS1*, *MET*, and *NTRK1/2/3*, with a median age at diagnosis of approximately 3 months. *ALK* fusions were the most prevalent (~40%), whereas *MET* fusions were rare, detected in only approximately 7% of cases. Subsequently, in 2020, Clarke et al[12] reported the methylation profiles, gene expression profiles, and nucleic acid sequencing results for 241 HGGs diagnosed in patients aged ≤4 years. This study also identified a unique class of HGG commonly diagnosed in patients aged <12 months (median age, ~3 months). The methylation profile of these infantile HGGs demonstrated significant segregation from other pHGGs in unsupervised t-distributed stochastic neighbor embedding (t-SNE) projections, but clustered along a continuum with desmoplastic infantile ganglioglioma/astrocytoma (DIG/DIA) (Figure 1). Transcriptomics of these infantile HGGs, now renamed as infant-type hemispheric glioma (IHG) in the 2021 *WHO Classification of Tumors of the CNS*, reported oncogenic fusions in RTKs (*NTRK1/2/3*, *ALK*, *ROS1*, and *MET*) at the 3′ end, with various genes as partners at the 5′ end, causing constitutive activation of the kinase domain and PI3K and/or MAPK pathways (Figure 2A, B). Despite the high frequency of RTK fusions (70%–80%) in the IHGs, 20% to 30% did not harbor gene fusions, and oncogenic drivers in these cases remain unknown.[1,12]

Although these studies were pivotal in the evolution of IHG as a distinct tumor entity in the 2021 *WHO Classification of Tumors of the CNS*, prospective data linking the newly defined IHG to its clinical correlates remained lacking. In 2024, Chiang et al[6] published results of the phase II SJYC07 trial for infants diagnosed with HGG between 2007 and 2017. Because these patients were treated under a single institutional protocol, curated clinical data—including treatment details, progression, clinical events, and cause of death—were available for all patients. DNA methylation and nucleic acid sequencing were performed on 56 cases histologically diagnosed as HGG (AA, n=14; glioblastoma, n=16; HGG, n=12; anaplastic pilocytic astrocytoma, n=1; high-grade pilomyxoid glioma, n=1; and HGNET, n=12), and the results were integrated with histopathology to yield an updated integrated diagnosis based on the 2021 *WHO Classification of Tumors of the CNS*. This reclassification split the 56 HGG into 4 tumor types: IHG (40%), pHGG (*H3K27M*-altered diffuse midline glioma, pHGG-MYCN, and pleomorphic xanthoastrocytoma; 11%), low-grade glioma (LGG; 7%), and other high-grade CNS tumors (16%). IHG was the most prevalent molecular group (n=22; 40%) and, consistent with the prior studies, arose in the cerebral hemispheres of the youngest patients (median age, 3 months [range, 0.0–4.4 years]), frequently harboring RTK gene fusions. The 5-year EFS and OS rates for the full cohort of 56 HGG cases were approximately 46% and 76%, respectively, comparable to outcomes reported in historical trials of infant HGGs (Table 1). Post hoc analysis using the updated classification revealed 5-year EFS and OS rates of 53.13% and 90.91% for IHGs, compared with 0.0% and 16.67% for other pHGGs (P=.0043 and P=.00013, respectively), indicating that accurate molecular–histopathologic diagnosis, rather than age at presentation, is essential in determining prognosis and survival in gliomas diagnosed during infancy and young childhood.

Current Diagnostic Approaches for IHG

Clinical Suspicion

IHG should be considered high on the differential diagnosis for congenital brain tumors detected on prenatal or postnatal imaging performed for macrocephaly or suspected neonatal stroke.[13–17] During the neonatal period and early infancy, progressively increasing head circumference, an intermittently bulging anterior fontanelle, and hemiparesis are often the first presenting symptoms in an otherwise well-appearing infant.[18,19] Due to the pliability of the skull, newborns and young infants may only develop late signs of increased intracranial pressure (ICP) when tumors reach a large volume or in the event of acute spontaneous hemorrhage. These patients frequently present in a critically ill state due to acute massive hemorrhage, elevated ICP, herniation, or brainstem compression, and may die acutely before, during, or after emergent neurosurgical management. Older infants and young children with IHG may present with new-onset afebrile seizures along with signs and symptoms of ICP and regression of milestones.[20–22]

Diagnostic Imaging

IHGs commonly demonstrate extensive hemorrhage, a key differentiating feature from other hemispheric tumors diagnosed in infancy.[6] On CT imaging, IHGs appear as peripheral, hemorrhagic, and mixed solid and cystic tumors in the cerebral hemisphere with severe mass effect and hydrocephalus. Although linear internal calcifications may be present, the coarse

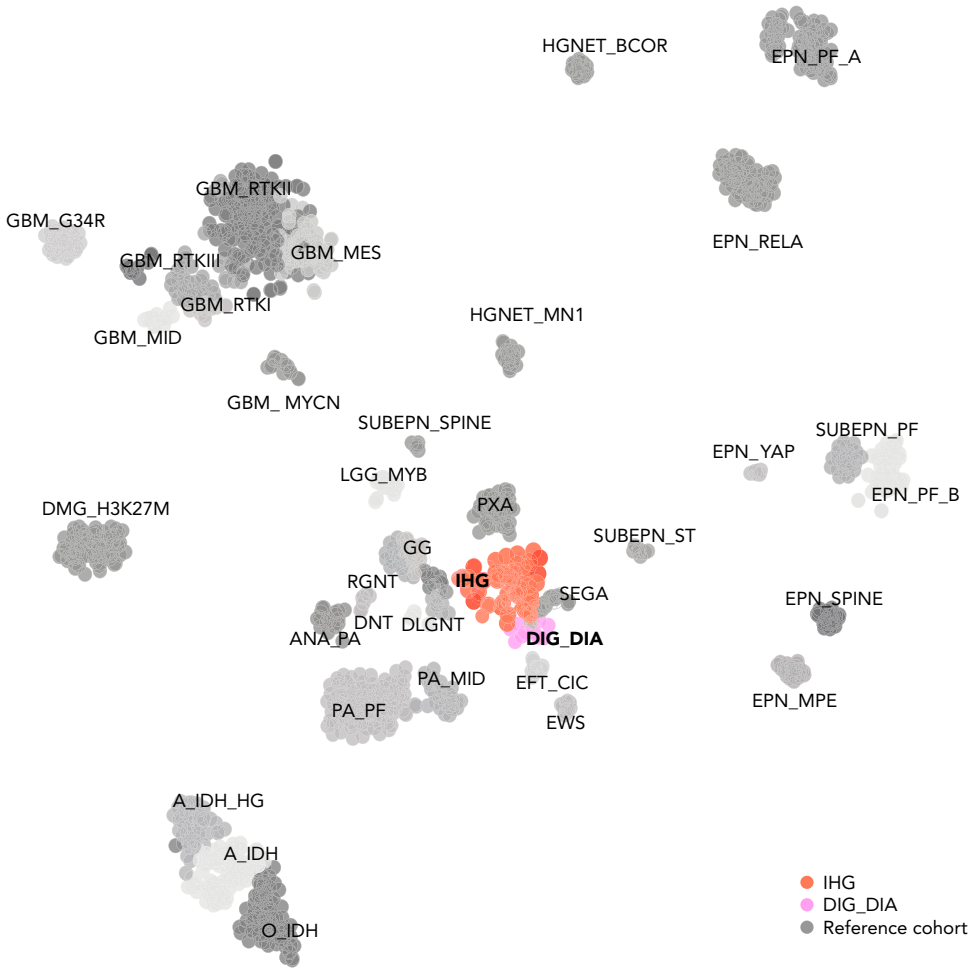

Figure 1. Scatter plot showing IHG (solid orange circles; institutional cases, n=30, and Capper et al[43] reference cohort, n=10) and DIG/DIA (solid pink circles; n=8) compared with 1,286 reference cases from Capper et al[43] (faded grey circles, n=1,238). Refer to Supplementary Table S1 for definitions of other abbreviations used in the figure.
Abbreviations: DIA, desmoplastic ganglioglioma/astrocytoma; DIG, desmoplastic ganglioglioma/astrocytoma; IHG, infant-type hemispheric glioma.

calcifications of supratentorial ependymomas are notably absent in IHGs (Figure 3A).[1]

On contrast-enhanced MRI, IHGs are well-circumscribed tumors with heterogeneously enhancing solid and nonenhancing cystic components, usually without distant leptomeningeal metastasis (Figure 3C, D). The solid regions are hemorrhagic, exhibiting heterogeneous T1 hyperintensity and T2 hypointensity, with corresponding susceptibility artifacts on gradient-echo (GRE) or susceptibility-weighted imaging (SWI) sequences (Figure 3B). The differential diagnosis on MRI includes DIG/DIAs, which are typically not hemorrhagic, and pleomorphic xanthoastrocytomas, which may have contiguous nodular leptomeningeal enhancement adjacent to the tumors typically not seen in IHGs.[23] Rarely, IHGs may present without internal hemorrhage, and are indistinguishable from DIG/DIAs on diagnostic imaging. This small subset of IHGs demonstrates solid components that are isointense to cortex on T1- and T2-weighted sequences, with homogeneous postcontrast enhancement (Figure 3E, F). A tissue diagnosis is essential to differentiate IHGs from DIG/DIAs in these scenarios.[24]

Standard MRI brain sequences, including pre- and postcontrast T1-weighted, T2-weighted, postcontrast fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging, and GRE or SWI, are essential for accurately characterizing these tumors. In our institutional experience, isotropic pre- and postcontrast T1 magnetization-prepared rapid gradient echo (MPRAGE) sequences with 1-mm slice thickness and subtraction imaging have demonstrated the highest yield for tumor characterization and operative planning for IHGs. GRE and SWI sequences are helpful in preoperative risk assessment to characterize the extent of intratumoral hemorrhage. Although, diffusion-weighted imaging is often limited by extensive hemorrhage, these sequences may be helpful for characterizing tumor cellularity in the small subset of nonhemorrhagic IHGs. Similarly, although leptomeningeal dissemination is uncommon, it must be routinely assessed and ruled out in all cases using a postcontrast FLAIR sequence.[6]

Integrated Histologic and Molecular Diagnosis

The histologic features of IHG exhibit significant variability, creating diagnostic challenges that are further compounded by the rarity of the disease. Before IHG was recognized as a distinct tumor type, it was diagnosed as glioblastoma or other HGGs, anaplastic ganglioglioma, DIA/DIG, ependymoma, or CNS primitive neuroectodermal tumor.[11,12,25–28] Histologically, IHGs are cellular

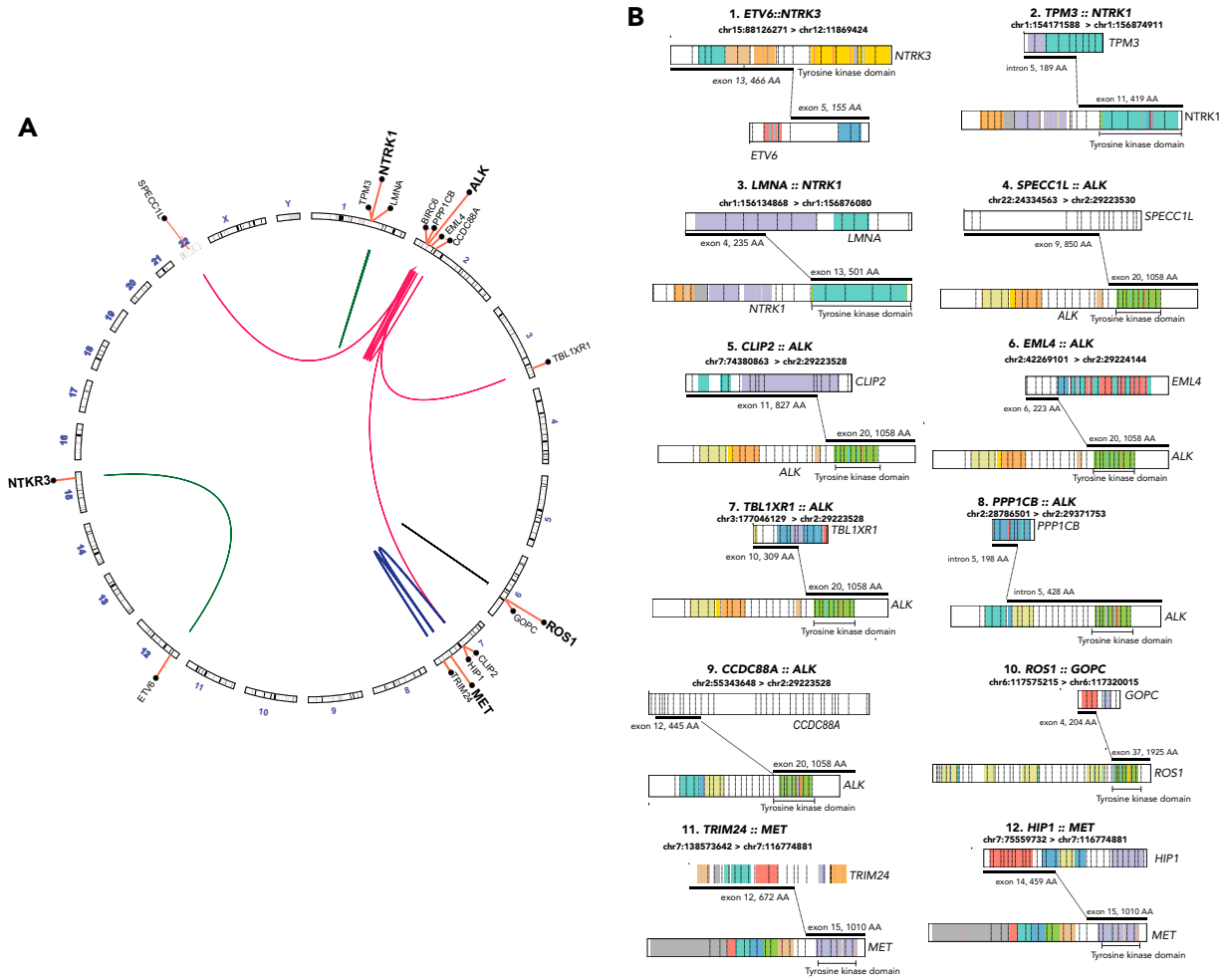

Figure 2. (A) Examples of common interchromosomal and intrachromosomal gene fusion in receptor tyrosine kinases (*ALK*, *NTRK1/3*, *ROS1*, and *MET*). **(B)** In-frame receptor tyrosine kinase fusion in infant-type hemispheric glioma. The kinase domains in all cases remain intact.

tumors (Figure 4A). They are generally well demarcated from the surrounding brain tissue, in contrast to other pHGGs, which exhibit diffusely infiltrative growth. IHGs commonly demonstrate local leptomeningeal involvement accompanied by intense desmoplastic reactions that can mimic the appearance of DIG/DIA. The astrocytic tumor cells can be spindle-shaped with fascicular growth, or epithelioid in appearance with distinct cytoplasmic borders, mild to moderate pleomorphism, and eccentric nuclei (Figure 4B). Ependymoma-like or papillary growth is also observed in some cases. Although typical IHGs are mitotically active with frequent pseudopalisading necrosis or microvascular proliferation, lower-grade–appearing areas are characteristically present and may lead to misdiagnosis in small biopsy samples. Additionally, tumor cells with ganglion cell differentiation are present in a subset of IHGs (Figure 4B).

Immunohistochemically, IHGs characteristically exhibit variable glial fibrillary acidic protein (GFAP) and OLIG2 expression (Figure 4C–D), unlike other pHGGs and LGGs that are typically strongly positive for both. Synaptophysin and neurofilament stains highlight the neoplastic ganglion cells in a subset of IHGs, in addition to demonstrating their noninfiltrative growth pattern (Figure 4E). Immunopositivity for ALK, NTRK1/2/3, or ROS1 proteins may suggest tumors harboring the respective gene fusions (Figure 4F). However, this immunoreactivity is not entirely specific and can also be seen in tumors lacking the corresponding gene fusions. Additionally, immunohistochemistry may fail to detect tumors in which the relevant epitopes are absent from the fusion proteins. Therefore, RNA sequencing remains the gold standard for confirming the gene fusions. IHG shares its immunophenotype with supratentorial ependymomas. The presence of prominent and widespread perivascular pseudorosettes should prompt consideration of this alternative diagnosis. In such scenarios, L1CAM immunoreactivity is useful in identifying *ZFTA*-fused ependymomas and differentiating them from IHGs.[29]

Given the high prevalence of RTK gene fusions in IHGs and their therapeutic implications, routine RNA sequencing for fusion detection should be considered in gliomas of very young children, both to aid in diagnosis and to guide treatment options. However, RTK gene fusions are not unique to IHG and can also be found in other HGGs and LGGs. Therefore, accurate diagnosis requires integration of histopathologic, immunophenotypical, and molecular findings. In cases of diagnostic uncertainty, DNA methylation profiling is useful in identifying IHG, particularly when samples are marginal or insufficient for next-generation sequencing, or in fusion-negative tumors. However, due to the

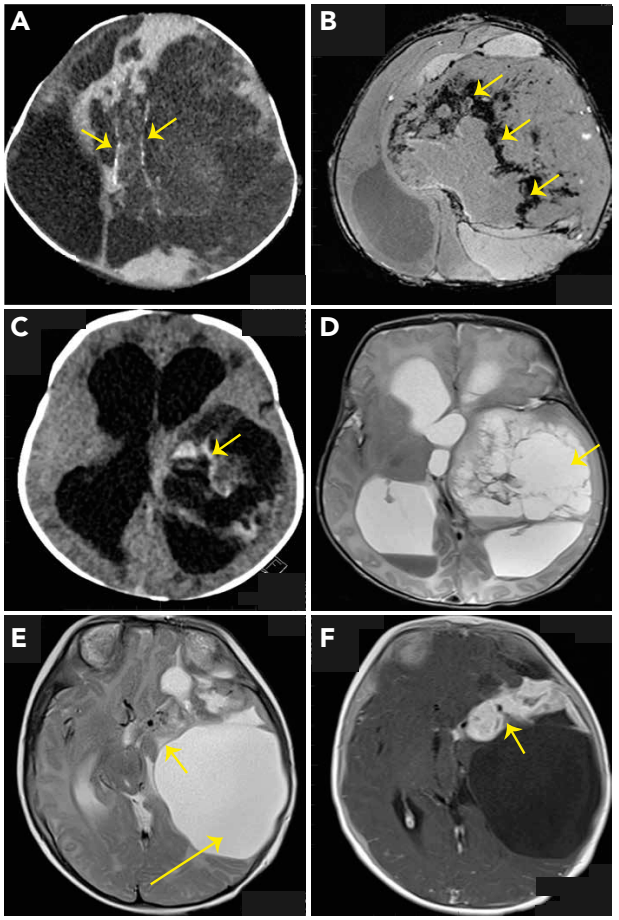

Figure 3. **(A)** Axial head CT of a 42-day-old male with enlarging head circumference showing a left hemispheric mass with linear calcification (arrow). **(B)** Axial GRE sequence of the same patient demonstrating extensive susceptibility artifact (arrows) representing microhemorrhage. **(C)** Axial head CT of a 21-day-old female with enlarging head circumference showing a left hemispheric mass with a hemorrhagic solid component (arrow). **(D)** Axial T2 image showing cystic components (arrow) in the same patient. **(E)** Axial T2 image of a 5-month-old male with an atypical left hemispheric IHG showing a medial, nonhemorrhagic solid component (short arrow) and peripheral cystic components (long arrow). **(F)** Axial postcontrast T1 MPRAGE sequence of the same patient demonstrating avid enhancement of the solid component (arrow).
Images are from unpublished cases treated within St. Jude Children's Research Hospital. Appropriate Institutional Review Board permission was obtained prior to use and submission of the data (IRB#21-08005).
Abbreviations: GRE, gradient-echo; IHG, infant-type hemispheric glioma; MPRAGE, magnetization-prepared rapid gradient echo.

rarity of IHG, the established reference cohorts for methylation profile classifiers may not fully or correctly capture its entire methylome spectrum, potentially affecting the sensitivity and specificity of classification algorithms. Furthermore, IHGs have a DNA methylation profile in a continuum with DIA/DIG, and intermediate examples exist, further confounding the effectiveness of DNA methylation profiling for diagnosis.

Challenges in IHG Management and the Role of Molecular Targeted Therapy

Survivors of IHG pay a heavy price for their cure. In an investigation assessing the neurologic and neurocognitive outcomes among 21 long-term IHG survivors, 76% had at least one neurologic sequela,

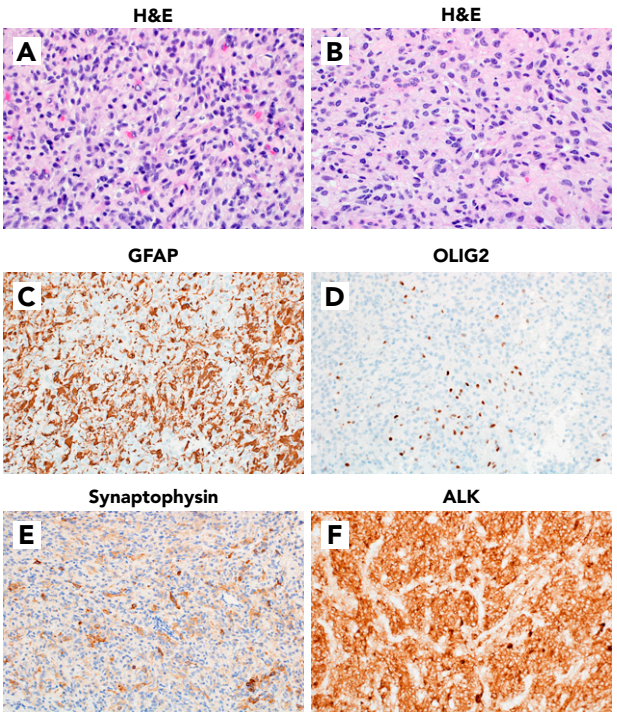

Figure 4. Histopathology of IHG. **(A)** IHG is characterized by high cellular density and a generally compact architectural pattern. Tumor cells display evident mitotic activity and variable cytologic features. **(B)** IHG often displays epithelioid morphology with focal areas of ganglion cell differentiation (center of image). Tumor cells typically show variable expression of **(C)** GFAP (clone 6F2) and **(D)** OLIG2 (clone 211F1.1). **(E)** Synaptophysin (clone 27G12) highlights tumor cells with ganglion cell differentiation. **(F)** Expression of the ALK fusion protein can be detected by immunohistochemistry (clone ALK01). All photos are from a 3-week-old female with a large frontoparietal mass harboring a *PPP1CB::ALK* fusion identified by RNA sequencing (original magnification, x200, for all).
Images are from an unpublished case treated within St. Jude Children's Research Hospital. Appropriate Institutional Review Board permission was obtained prior to use and submission of the data (IRB#21-08005).
Abbreviations: GFAP, glial fibrillary acidic protein; H&E, hematoxylin-eosin; IHG, infant-type hemispheric glioma.

including paresis, plegia, spasticity, and dysarthria, and >50% had a long-term seizure disorder. Patients aged <6 months at diagnosis had higher rates of dysarthria compared with older infants (P=.019). The median IQ for the entire cohort was significantly lower than the standard (68.0), and age <6 months at diagnosis was associated with lower IQ.[12,29]

Although the poor quality of life may be related to nonmodifiable factors such as very young age at presentation, the impact of cancer-directed treatment on long-term morbidity is not trivial. Extensive review of neurosurgical records from 30 craniotomies in 16 patients with IHG showed that 43% were complicated by massive intraoperative blood loss requiring transfusion, and 13% required intraoperative resuscitation for hypovolemic shock, resulting in cessation of surgery. Of the 10 patients who required >1 craniotomy during their treatment course, 4 (40%) underwent reoperation due to postoperative complications from the initial surgery, including postsurgical intertumoral hemorrhage and large-volume blood loss from resection bed hemorrhage.[5] To reduce surgical morbidity, neoadjuvant chemotherapy has been sporadically employed in infantile tumors to achieve

devascularization and cytoreduction of volumetrically large masses prior to resection.[30,31] Overall, although approximately 70% to 80% of patients with IHG survive, the high acute surgical morbidity and compromised quality of life raise questions about the continued use of upfront maximal surgical resection followed by chemotherapy.

Driven by unique RTK fusions in an otherwise genomically silent background, IHGs represent excellent candidates for targeted therapy with tyrosine kinase inhibitors (TKIs).[2,5] Preclinical studies in animal models of IHG have demonstrated efficacy and improved survival with TKI treatment,[12,32] and early-phase tissue-agnostic clinical trials have reported promising activity of TKIs in refractory pediatric brain tumors harboring RTK fusions.[33–36]

Published reports provide proof of concept for TKI use in patients with IHG.[18–22,37–40] One of the earliest examples involved a 3-year-old patient with *ALK* fusion–positive IHG who underwent 2 unsuccessful attempts at maximal surgical resection and became critically ill due to an intracranial bleed. Lorlatinib, a third-generation ALK kinase inhibitor, was administered via a nasogastric tube, resulting in rapid cytoreduction of the large hemispheric tumor and enabling a safe gross total resection.[41] Similarly, several cases of successful therapeutic response to TKIs, including entrectinib[18] and larotrectinib,[27,37,38,42] have been in *NTRK1/2/3* and *ROS1* fusion–positive IHGs. However, the use of CNS-penetrant MET inhibitors, such as cabozantinib and capmatinib, remains understudied in this rare population. This is likely due to the extreme rarity of MET fusions in IHG and the limited data on the pediatric dosing and safety profiles of these agents. Recently, capmatinib was reported to have superior brain pharmacokinetic properties and improved in vitro and in vivo efficacy in patient-derived MET-driven IHG xenografts compared with cabozantinib and crizotinib.[32] However, pediatric-specific clinical data remain lacking. Despite the increased use of TKIs in IHG, critical questions regarding their safety, optimal timing and duration of therapy, and long-term toxicity profile in this vulnerable population remain unanswered. Furthermore, reported cases of tumor relapse following TKI discontinuation indicate that, although targeted therapy has efficacy in early disease control, its curative potential remains unestablished.[41] Therefore, although it may be tempting to use TKIs as a primary treatment, this approach should first be evaluated within the framework of a molecularly targeted, multi-strata frontline clinical trial before being established as standard of care. Current active clinical trials enrolling patients with IHG are either tissue-agnostic (ClinicalTrials.gov identifier: NCT04589845) or inhibitor-specific (NCT04655404, NCT04774718, NCT06528691) and offer limited potential to establish standardized IHG-specific treatment. Despite these limitations, we believe that this very rare patient population is best treated and monitored within the context of controlled, well-regulated clinical trials, especially when TKIs are being considered based on fusion status. In the absence of suitable clinical trials, IHGs should be managed at centers with access to a pediatric neurocritical ICU and an experienced multidisciplinary team, including pediatric neurosurgeons, pediatric neuro-oncologists, neuroradiologists, and expert neuropathologists, to facilitate time-sensitive clinical decisions and diagnosis.

Conclusions

IHG is a distinct tumor type most prevalent in first year of life and is genomically driven by RTK fusions, which serve as potential therapeutic targets. Although patients generally achieve good overall survival with RT-sparing treatment, survivors often experience significant long-term neurocognitive and neurologic impairments. TKIs have demonstrated excellent efficacy in early tumor control and cytoreduction, but their curative potential remains unexplored. Therefore, there is a critical need for IHG-specific well-monitored, and collaborative frontline clinical trials incorporating molecularly guided treatment to improve both cure rates and long-term outcomes in infants with IHG.

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