

FALL 2026

Blood-Brain Barrier Development and Treatment Response in Pediatric Brain Tumors: A Review

By Madeleine Yang

AUTHOR BIOGRAPHY

Madeleine Yang is a rising sophomore at Phillips Academy in Andover, Massachusetts. She is passionate about neuroscience, oncology, and biology, and hopes to expand her knowledge on these subjects.

ABSTRACT

Pediatric brain tumors remain a leading cause of cancer-related mortality in children, partially due to ineffective delivery of systemic therapies across the blood-brain barrier (BBB). Unlike adults, the pediatric blood-brain barrier (BBB) in infants undergoes significant postnatal maturation during the first year of life, resulting in age-dependent differences in permeability, transporter expression, and barrier regulation. The project examines how BBB immaturity and blood-brain tumor barrier (BBTB) heterogeneity influence the delivery discrepancy, efficacy and toxicity of antitumor drugs (chemotherapy, targeted therapies, and radiation), and the development of emerging, novel antitumor drug delivery tools for infantile brain tumors. This review distinguishes between the developing physiological BBB and the pathological BBTB, which may exhibit regionally increased or decreased permeability depending on tumor biology. Through a structured review of current literature, the study aims to identify why therapeutic strategies for adult brain tumor patients fail to translate to pediatric brain tumor populations and highlight clinical implications of the BBB in drug resistance, toxicity, and therapeutic design.

Keywords: *pediatric tumors, infants, drug efficacy, blood-brain barrier, brain tumors, drug delivery, brain tumor therapy, BBB maturation, blood-brain tumor barrier*

Pediatric brain tumors are the most prevalent solid tumors—abnormal masses of brain tissue that exclude hematologic cancers—and the leading cause of cancer-related mortality in children, with brain tumors in infants representing a disproportionately high share of pediatric central nervous system (CNS) tumors

(National Brain Tumor Society, 2026; Shah et al., 2025). Unlike adult brain tumors, pediatric brain tumors arise in a developing CNS, characterized by dynamic neurovascular remodeling—the structural and functional changes in interactions between neural and vascular systems—and ongoing myelination, a process that regulates brain communication and maturation of regulatory brain structures (Federici et al., 2025). These developmental differences influence tumor biology and therapeutic response, making pediatric brain tumors fundamentally distinct from their adult counterparts.

A critical determinant of treatment efficacy is the BBB, an endothelial barrier that regulates and prevents molecular transport into the brain. The BBB severely limits the penetration of many neurotoxins, proteins, or xenobiotics, including >90-98% (depending on estimate) of small-molecule drugs and most macromolecular therapeutics, posing a major challenge for treating brain tumors (Abbott et al., 2010). In pediatric brain tumors, BBB integrity is highly heterogeneous and varies by tumor subtype, molecular profile, and anatomic location, contributing to inconsistent or ineffective drug delivery (Gao et al., 2025). The blood–brain tumor barrier (BBTB) refers to tumor-associated modifications of the BBB that create spatially heterogeneous permeability ranging from intact to highly disrupted regions (Morris et al., 2023). Studies describing BBB developmental mechanisms emphasize the importance of cellular interactions within the neurovascular unit in maintaining barrier integrity.

Like many anatomical structures, the pediatric BBB has major discrepancies from an adult BBB. Contrary to the assumption that BBB immaturity uniformly increases permeability, developmental changes in efflux transporters and neurovascular signaling can maintain or even restrict CNS drug exposure while altering susceptibility to toxicity (Eng et al., 2022). The blood-brain barrier is formed by specialized endothelial cells interconnected by tight junctions, which are composed of transmembrane proteins like claudin and occludin to create a seal that forces substances to pass through cells instead of in between them (Abbott et al., 2010). The BBB is supported by pericytes, cells embedded in the capillaries of the BBB, and astrocytic end-feet, specialized glial cell structures that envelop BBB blood vessels, both of which help to regulate molecular transport between the circulation and neural tissue (Eltanahy et al., 2021). During the developing stages of the blood-brain barrier, its structural components are not fully formed (Federici et al., 2025). The barrier therefore undergoes progressive maturation, with tight junctions, transporters, pericytes, and astrocytes establishing functional integrity (Kuo & Majd, 2020). This developmental immaturity alters permeability, efflux capacity, and susceptibility to toxicity, rendering adult BBB models insufficient for predicting drug behavior in infants and young children (Gao et al., 2025).

In addition to structural maturation, BBB permeability is also affected by specialized transporter expression on endothelial cells and pericytes. Efflux transporters such as P-glycoprotein and other ATP-binding cassette (ABC) transporters are increasingly expressed during fetal and postnatal development, contributing to

protection of the developing brain from xenobiotics and circulating toxins. These ABC transporters are overexpressed in tumors, actively effluxing therapeutic agents out of tumor cells, leading to reduced intracellular drug accumulation and limited drug penetration into the CNS (Amawi et al., 2025). Research examining fetal and neonatal models suggests that these transport systems may significantly influence the pharmacokinetics of therapeutic agents administered during early life (Eng et al., 2022). Pericytes also stabilize the barrier and regulate its permeability. These structures are crucial for the regulation of BBB properties and influence tight junction integrity and drug transport activity. BBB function—particularly the regulation of permeability and tight junction integrity—emerges through interactions between endothelial cells and pericytes (Eltanahy et al., 2021).

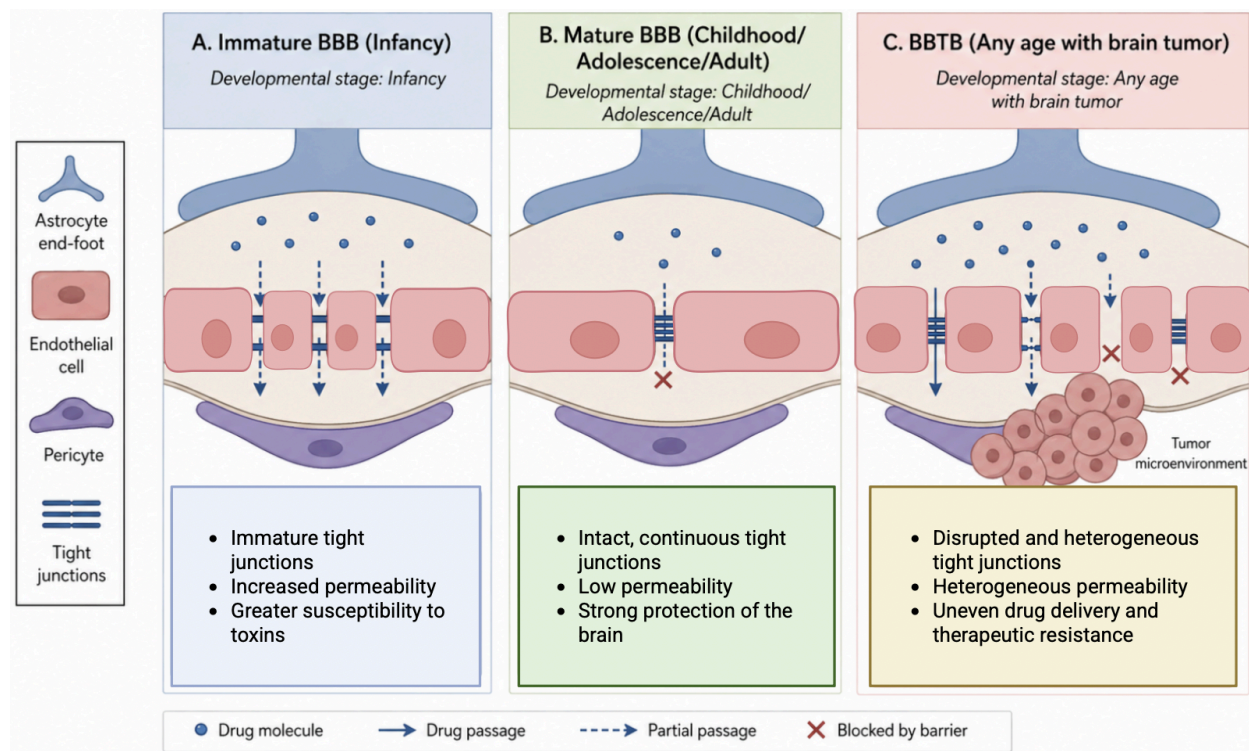
Tumor subtype further modulates BBB properties, often exerting greater impact on permeability than histological grade. Certain pediatric tumors, like medulloblastomas, cause a highly permeable BBB, while others, including diffuse midline gliomas, retain an intact and restrictive barrier. This spatial and molecular heterogeneity of the BBB results in differential drug penetration and distribution and contributes to therapeutic failure for pediatric brain tumors (Gao et al., 2025).

Both developmental BBB maturation and tumor-associated neurovascular modulation represent a major clinical challenge. While strategies to modulate the BBB may enhance permeability and therapeutic delivery, they also pose potential neurodevelopmental risks in children due to the vulnerability of the developing brain (Federici et al., 2025). Accordingly, this research seeks to determine how immaturity of the pediatric BBB alters the penetration, efficacy, and toxicity of cancer therapies compared with older children and adults. In infants, BBB immaturity interacts with tumor-driven vascular heterogeneity to produce non-uniform drug delivery, enhanced efflux-mediated resistance, and increased neurotoxicity risk, rather than consistently improving therapeutic penetration (Gao et al., 2025). Thus, this study makes it essential to better understand the interplay between developmental BBB maturation, tumor-associated modulation of BBB biology and the BBB permeability of antitumor drugs for optimizing therapeutic strategies in pediatric brain tumors.

Elucidating developmental differences in BBB structure and function is critical for improving survivorship and life quality for pediatric brain tumor patients, as treatment-related neurotoxicity can have lifelong consequences (Gao et al., 2025). Insights into age-dependent barrier properties may inform the tailored design of safer and more effective therapeutic strategies, including age-appropriate drug selection, dosing, and delivery approaches. Ultimately, this knowledge has important implications for pediatric neuro-oncology by guiding the translation of therapies that account for both tumor biology and the unique vulnerabilities of the developing brain.

Figure 1

Conceptual Model (Adult BBB, Infant BBB, and BBTB Drug Delivery Schematic)



Note. This model reads as a comparison of the immature infant BBB, mature BBB, and BBTB. The infant BBB exhibits incomplete tight junction development and increased permeability. The mature BBB maintains tight junction integrity and restricts molecular transport. The BBTB demonstrates heterogeneous disruption of barrier structure, resulting in uneven drug delivery and contributing to therapeutic response. Created by author with BioRender.com, 2026.

METHODOLOGY

This study was conducted in accordance with PRISMA 2020 guidelines for systematic reviews and meta-analyses. The protocol was developed prior to the literature search.

FALL 2026

A systematic literature search was performed using PubMed and IEEE Xplore from screening of 2020-2026 papers. The search strategy included combinations of the following keywords or synonyms and Medical Subject Headings (MeSH): blood-brain barrier, pediatric tumors, brain tumors, drug delivery, brain tumor therapy, and BBB maturation. Boolean operators (AND, OR) were used to combine search terms.

Eligibility Criteria**Inclusion Criteria**

- Studies on infants, neonates, or pediatric patients
- Studies about BBB development, permeability, or transporters
- Brain tumors (glioma, medulloblastoma, DMG, etc.)
- Drug delivery, therapy resistance, or toxicity
- Human + relevant animal models
- Published 2020–present

Exclusion Criteria

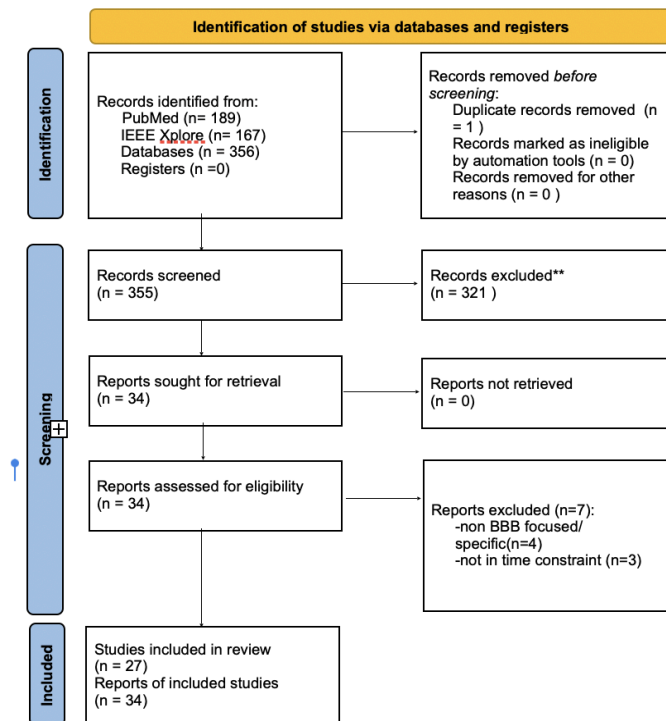
- Adult-only studies
- Not about BBB
- Not CNS tumors
- Editorials/opinions (unless background)
- Non-peer-reviewed

All search results were exported to MyBib and duplicates were removed. Titles and abstracts were screened for relevance. Full-text articles were subsequently assessed for eligibility based on the predefined inclusion and exclusion criteria.

The study selection process is summarized in Figure 2. A total of 356 records were identified through database searches.

Figure 2*PRISMA Flow Diagram*

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

This work is licensed under CC BY 4.0. To view a copy of this license, visit <https://creativecommons.org/licenses/by/4.0/>

Note. PRISMA flow diagram illustrating study identification, screening, eligibility assessment, and inclusion. Created by author, 2026.

Data was extracted from each eligible article using a standardized form. Fields taken into consideration: Author, year, key findings. Extracted data included study characteristics, experimental model, drug delivery approach, and reported outcomes.

RESULTS

A total of 356 records were identified through database searches in PubMed and IEEE Xplore. After removal of 1 duplicate record, 355 studies remained for screening. Titles and abstracts were screened for relevance, resulting in the exclusion of 321 records that did not meet inclusion criteria (e.g., adult-only populations, non-CNS tumors, or lack of relevance to BBB function or drug delivery).

The remaining 34 full-text articles were assessed for eligibility. Of these, 7 were excluded for the following reasons: 4 because they were not BBB focused and 3 were in the wrong time window.

Ultimately, 27 studies met all inclusion criteria and were included in the final analysis.

The screening process followed PRISMA guidelines and was conducted independently prior to full-text review.

Studies were coded into thematic categories; some studies contributed to multiple categories. Of the full-text screened sources, 21 studies focused on the core search, 5 are focused on drug delivery, 7 investigate the developmental BBB, and 1 reviews heterogeneity.

Thematic Findings

Tumor Biology and Microenvironmental Heterogeneity

BBB immaturity sets the baseline permeability landscape, but tumor-specific vascular remodeling reshapes the landscape into a heterogeneous BBTB, ultimately determining drug access (Morris et al., 2023; Gao et al., 2025).

Pediatric brain tumors are biologically distinct from adult tumors and cannot be directly compared, yet both demonstrate heterogeneity in their BBTBs. In pediatrics, unique genetic alterations (tumor mutations) influence tumor growth, vascularization, and therapy response (Bonada et al., 2024; Di Ruscio et al., 2022; Miguel Llordes et al., 2023; Suter et al., 2020). Studies indicate that specific brain tumors, such as diffuse midline gliomas and hemispheric high-grade gliomas exhibit molecular heterogeneity driven by mutations in histone proteins, which are released during cellular injuries (like tumors), creating BBB leakage, reduced tight junctions, and generally weakening the BBB (Bonada et al., 2024; Di Ruscio et al., 2022; Miguel Llordes et al.,

2023). This molecular diversity contributes to variable BBB integrity across tumor regions, as tumor biology affects local vascular permeability and transporter expression.

Epigenetic plasticity further complicates tumor behavior. Tumor cells can dynamically alter gene expression in response to environmental cues or therapeutic pressure, creating resistant subpopulations that survive treatment. These cellular and molecular factors collectively shape the BBTB, which differs significantly from the intact BBB and varies within the same tumor (Morris et al., 2023). The BBTB is a modulated barrier in which BBB integrity is variably altered, ranging from highly permeable to functionally intact depending on tumor region and subtype, which can impede delivery of therapeutic agents to the tumor cells (Rechberger et al., 2025).

Tumor microenvironmental heterogeneity is another critical determinant of therapeutic response. Variable speeds of maturation for different structures, like tumor cells, endothelial cells, pericytes, and extracellular matrix components modulate barrier permeability. Consequently, drug delivery across the BBTB is often inconsistent, as some tumor regions maintain an intact barrier while others are more permeable (Morris et al., 2023; Fernando et al., 2024). These variations help explain why conventional chemotherapy and targeted therapies frequently fail to achieve uniform efficacy in pediatric brain tumors (Malik et al., 2023; Fernando et al., 2024).

Overall, the sources highlight that tumor genetic diversity, epigenetic plasticity, and microenvironmental interactions collectively contribute to heterogeneity in barrier structure, function and drug accessibility. Understanding these factors is essential for developing tailored strategies to improve therapeutic delivery and efficacy in pediatric brain tumor patients (Morris et al., 2023; Suter et al., 2020; Bonada et al., 2024; Fernando et al., 2024).

Emerging Strategies to Overcome the BBB

Given the significant limitations imposed by the BBB and BBTB, recent research has focused on developing strategies to enhance drug delivery. In order to provide effective cancer treatments for pediatric brain tumors, figuring out how to overcome the BBB is crucial. Evaluating the BBB permeability of potential drugs is critical for drug discovery and development, especially for enhancing the effectiveness of CNS medications (Chu et al., 2025).

Some advanced technologies contribute to this goal by temporarily opening the BBB through increasing its permeability (Fileri et al., 2025; Martinez et al., 2024; Thavarajasingam et al., 2023). These advanced technologies include physical methods like focused ultrasound, nanoparticle-focusing

nanotechnology, and receptor-mediated transcytosis (RMT), to deliver therapeutics to the central nervous system (Haumann et al., 2020; Rahman et al., 2023; Vanbilloen et al., 2023).

In DMGs, focused ultrasound technology is able to penetrate the BBB by non-invasively permeabilizing it for a small focal region with millimeter precision (Martinez et al., 2024). The treatment enables targeted drug delivery within those small regions, which is important for characteristically impermeable tumor vessel regions of the BBB. Despite this breakthrough treatment method, there are still some experimental and safety concerns because of the sheer invasiveness of the procedure (Thavarajasingam et al., 2023).

Another method is the usage of nanoparticle-based drug delivery (Abballe et al., 2023; Vanbilloen et al., 2023; Si et al., 2025; Yang et al., 2021; Hsu et al., 2021). Tiny organic (liposomes, micelles) and inorganic (gold, silica) nanoparticles are engineered with surface modifications to directly bypass the BBB or bind to BBB receptors to enhance permeability. The potential challenge for nanoparticles-based drug delivery is often associated with the stability in circulation and long-term toxicity, potentially limiting their application (Omidian & Mfofo, 2023).

Receptor-mediated Transcytosis (RMT) uses ligands (antibodies, peptides and aptamers) to target receptors on the BBB surface, such as the transferrin receptor (TfR), LDL receptor, and insulin receptor to mediate drug transcytosis, promoting BBB penetration and brain delivery (Haumann et al., 2020). The combination of ligand-guided specific BBB targeting via RMT and specific tumor cell targeting of antitumor drugs (antibody-based immunotherapy) enable increased accumulation of antitumor drugs in diseased tissue cells while sparing healthy cells, improving therapeutic efficacy and minimizing the off-target toxicity (Abballe et al., 2023; Vanbilloen et al., 2023).

Alternative delivery methods bypass the BBB entirely, such as CED, convection-enhanced delivery, and direct infusion techniques (Fredricks et al., 2026; Haumann et al., 2020; Rahman et al., 2023). CEDs enable direct, intraparenchymal placement of therapeutics that bypass the BBB, allowing for high local drug concentration. However, CED remains a developing treatment option, and the accuracy of drug delivery is critical for preventing the unintended spread of therapeutic agents (Fredricks et al., 2026). Other methods like intranasal delivery and intra-arterial drug delivery, which administer drugs directly into a structure near the tumor, are also effective in avoiding the interference of the BBB (Haumann et al., 2020).

Pharmacological and molecular strategies are means for improving drugs themselves or targeting BBB biology to improve treatment efficacy. Specifically for safety in infants and children, these drugs must be repurposed to have a favorable profile of BBB penetration, proven efficacy in preclinical models of tumors of interest, and pharmacokinetic properties that allow therapeutically effective concentrations at the tumor site.

FALL 2026

Non-oncology related drugs are able to be repurposed to bypass the BBB in therapeutic concentrations or avoid efflux (Rechberger et al., 2025). Because ABC transporters hinder the penetration of drugs into the CNS, ABC inhibitors were developed but ultimately failed to be implemented due to safety concerns and limited clinical success, as disrupting efflux pumps caused dangerous toxicity (Amawi et al., 2025). Some current research investigates combining tyrosine kinase inhibitors (TKIs)–targeted cancer therapies that block enzymes responsible for cancer growth– with other treatments, as certain TKIs (e.g., Nilotinib, Gefitinib) can also modulate ABC transporters (Fernando et al., 2024). Therefore, drugs that can potentially inhibit multiple ABC transporters temporarily could represent another approach (Amawi et al., 2025).

Recent advances have explored the use of artificial intelligence and computational modeling to improve drug delivery across the blood–brain barrier. Machine learning approaches, including graph neural networks, have been developed to predict the permeability of therapeutic compounds and identify molecular features that facilitate BBB penetration. These models have the potential to optimize drug design prior to in vivo testing, although they remain in early stages of development and require further validation for clinical application (Vodilovska et al., 2025).

Despite promising advances, many of these approaches remain in early stages, highlighting the need for continued research to optimize safe and effective BBB-targeted therapies for pediatric populations.

DISCUSSION

Compare/Contrast of Sources

The findings of the review suggest that BBB immaturity in infants does not uniformly enhance drug delivery. Instead, it interacts with tumor-specific vascular heterogeneity to produce non-uniform drug distribution, efflux-mediated resistance, and increased risk of neurotoxicity. While some studies describe the BBB as a significant obstacle that limits therapeutic penetration, others report regions of increased permeability within tumor tissue that may permit drug entry. At first glance, these findings appear contradictory; however, they can be reconciled by considering the heterogeneity of the BBTB. Evidence suggests that BBB integrity is not uniform across tumors, with some regions maintaining an intact barrier while others exhibit varying degrees of disruption. This variability leads to inconsistent drug distribution and helps explain why therapeutic responses are often unpredictable. Rather than representing conflicting conclusions, the literature collectively supports a model in which BBB and BBTB heterogeneity is a central determinant of treatment efficacy in pediatric brain tumors (Morris et al., 2023; Gao et al., 2025; Malik et al., 2023; Haumann et al., 2020).

FALL 2026

Interaction between BBB and Tumor Heterogeneity

Beyond barrier-level variability, intrinsic tumor heterogeneity further complicates treatment in pediatric brain tumors. Differences in genetic mutations across tumor cells contribute to variability in therapeutic response, as not all cell populations respond uniformly to treatment. Diffuse midline gliomas, for example, frequently harbor histone mutations (H3 variants) that drive epigenetic alterations in gene expression. These changes can affect immune-related pathways and modify the tumor microenvironment, thereby contributing to variability in tumor behavior and treatment outcomes (Bonada et al., 2024). In addition to genetic diversity, epigenetic plasticity, even when initial treatment responses are observed, may result in resistant subpopulations emerging over time, leading to disease progression (Suter et al., 2020). Furthermore, the tumor microenvironment, a complex, supportive ecosystem surrounding tumors consisting of cancer cells, immune cells, normal neural cells, and blood vessels, plays a critical role in directly influencing drug penetration and distribution to shape BBB and BBTB integrity (Morris et al., 2023; Fernando et al., 2024). The clinical consequences of tumor heterogeneity are significant. Variability in barrier function leads to uneven drug delivery, while the presence of resistant tumor subpopulations limits overall treatment effectiveness. Consequently, therapeutic success is often partial or difficult to predict, and disease recurrence remains common even when drugs are able to reach the tumor. These findings support a model in which BBB immaturity does not act as a simple permeability modifier, but instead determines the baseline vascular state upon which tumor-driven remodeling creates highly context-dependent drug access landscapes.

Clinical Implications

Although numerous strategies have been developed to bypass or modulate the BBB, their application in pediatrics—specifically in infants—remains a risk. While these targeted approaches show promise in enhancing drug delivery and overcoming the BBB, they may not be as equally safe in developing brains. The infant BBB is still undergoing structural maturation, so it is more vulnerable to toxins and the off-target effects of therapeutic agents. Disrupting this fragile BBB may compromise its protective function and pose risks to neurodevelopment because of its function as a stable, protective environment that ensures proper neuronal growth. In addition, alterations in regulated transport systems (ABC transporters) induce lasting effects on barrier function and brain homeostasis (Eng et al., 2022). These considerations highlight the need for extra caution when applying BBB-targeting therapies to pediatric patients and underscore the importance of developing age-specific treatment strategies.

Pediatric Application Risks

FALL 2026

Despite promising advances in research, important gaps remain in the application of BBB- targeting therapies to pediatric populations (Rahman et al., 2023). In particular, there is a lack of pediatric-specific model counterparts for brain tumor treatments, limiting the ability to accurately predict therapeutic efficacy and toxicity in children (Morris et al., 2023). Additionally, long-term safety data remains sparse, raising concerns about the potential neurotoxic and developmental side-effects in the developing brain. Clinical translation is further hindered by insufficient trials evaluating these approaches in children, restricting evidence based optimization of treatment protocols. Therefore, more age-dependent treatment strategies and personalized approaches are needed to account for differences in developing barrier function and tumor biology (Rahman et al., 2023; Thavarajasingam et al., 2023; Filieri et al., 2025). Addressing these gaps will be critical for improving therapeutic outcomes in pediatric brain tumor patients.

CONCLUSION

The evidence reviewed suggests that developmental BBB maturation is not merely a background physiological process but a critical determinant of therapeutic delivery and treatment response in pediatric brain tumors. Future therapies must integrate knowledge of age-specific BBB biology with tumor-specific targeting strategies to achieve safe and effective treatment outcomes in infants.

LIMITATIONS OF THE REVIEW

The review has several limitations that should be considered when interpreting the findings. First, the study is conducted based on a limited number of available pediatric-specific sources, particularly those focused on infants and developmental stages. As a result, some conclusions rely on extrapolation of studies on older pediatric patients or animal models, which may not fully capture the unique characteristics of the infant BBB. Limited availability of clinical trials on drug penetration and long-term outcomes in pediatric patients restricts the ability to accurately determine the safety, efficacy, and developmental impact of BBB-targeting therapies in infants. Additionally, the review is constrained by a time frame of 2020- present, which, while ensuring relevance, may exclude foundational research. Taking these limitations into consideration as the review is perused assures a fuller scope of understanding.

ACKNOWLEDGEMENTS

The author thanks Dr. Julia Kang and Dr. Pengcheng Zhou for reviewing the manuscript and providing helpful feedback.



SCHOLARLY REVIEW JOURNAL

E-ISSN: 2996-8380

Published by Leadership & Innovation Lab

FALL 2026

The author acknowledges the use of AI tools, including ChatGPT, to assist with organizing sources, as well as citation tools such as MyBib for formatting references and BioRender AI for constructing diagrams. All content and analysis were independently written and verified by the author.

REFERENCES

- Abballe, L., Spinello, Z., Antonacci, C., Coppola, L., Catanzaro, G., & Miele, E. (2023). Nanoparticles for Drug and Gene Delivery in Pediatric Brain Tumors' Cancer Stem Cells: Current Knowledge and Future Perspectives. *Pharmaceutics*, 15(2), 505. <https://doi.org/10.3390/pharmaceutics15020505>
- Abbott, N. J., Patabendige, A. A., Dolman, D. E., Yusof, S. R., & Begley, D. J. (2010). Structure and function of the blood–brain barrier. *Neurobiology of Disease*, 37(1), 13–25. <https://doi.org/10.1016/j.nbd.2009.07.030>
- Amawi, H., Hammad, A. M., Hall, F. S., Hussein, N., Rataan, A. O., Mrayyan, A., Alkasasbeh, M., Abu-Qatouseh, L., Tooze-Hobson, P., & Tiwari, A. K. (2025). Revisiting strategies to target ABC transporter-mediated drug resistance in CNS cancer. *Cancer Biology & Medicine*. <https://doi.org/10.20892/j.issn.2095-3941.2024.0492>
- Bonada, M., Pittarello, M., De Fazio, E., Gans, A., Alimonti, P., Slika, H., Legnani, F., Di Meco, F., & Tyler, B. (2024). Pediatric hemispheric high-grade gliomas and H3.3-G34 mutation: A review of the literature on biological features and new therapeutic strategies. *Genes*, 15(8), 1038. <https://doi.org/10.3390/genes15081038>
- Chu, S., Duan, G., & Yan, C. (2025). Multi-relational graph neural network with collaborative constraints for predicting blood–brain barrier permeability of small molecule drugs. In *Proceedings of the 2025 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)* (pp. 639–644). IEEE. <https://doi.org/10.1109/BIBM66473.2025.11357198>
- Di Ruscio, V., Del Baldo, G., Fabozzi, F., Vinci, M., Cacchione, A., de Billy, E., Megaro, G., Carai, A., & Mastronuzzi, A. (2022). Pediatric diffuse midline gliomas: An unfinished puzzle. *Diagnostics*, 12(9), 2064. <https://doi.org/10.3390/diagnostics12092064>
- Eltanahy, A. M., Koluib, Y. A., & Gonzales, A. (2021). Pericytes: Intrinsic transportation engineers of the CNS microcirculation. *Frontiers in Physiology*, 12, 719701. <https://doi.org/10.3389/fphys.2021.719701>
- Eng, M. E., Imperio, G. E., Bloise, E., & Matthews, S. G. (2022). ATP-binding cassette (ABC) drug transporters in the developing blood–brain barrier: Role in fetal brain protection. *Cellular and Molecular Life Sciences*, 79(8), 415. <https://doi.org/10.1007/s00018-022-04432-w>

FALL 2026

- Federici, L., Cisternino, S., Auvity, S., Gelot, A., Becmeur-Lefebvre, M., Favier, M., Letort, G., Mailly, P., Cohen-Salmon, M., & Boulay, A.-C. (2025). Perinatal maturation of drug transporters and claudin-5 at the blood–brain barrier. *CNS Neuroscience & Therapeutics*, 31(9), e70614. <https://doi.org/10.1111/cns.70614>
- Fernando, D., Ahmed, A. U., & Williams, B. R. G. (2024). Therapeutically targeting the unique disease landscape of pediatric high-grade gliomas. *Frontiers in Oncology*, 14, 1347694. <https://doi.org/10.3389/fonc.2024.1347694>
- Filieri, S., Miciaccia, M., Armenise, D., Baldelli, O. M., Liturri, A., Ferorelli, S., Sardanelli, A. M., Perrone, M. G., & Scilimati, A. (2025). Can Focused Ultrasound Overcome the Failure of Chemotherapy in Treating Pediatric Diffuse Intrinsic Pontine Glioma Due to a Blood–Brain Barrier Obstacle? *Pharmaceuticals*, 18(4), 525. <https://doi.org/10.3390/ph18040525>
- Fredricks, N. S., Harkins, M., Price, A., Morden, F. T., & Dewan, M. C. (2026). Protocols and safety profile of convection enhanced delivery in pediatric patients: a systematic review. *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery*, 42(1), 30. <https://doi.org/10.1007/s00381-025-07121-8>
- Gao, Q., Song, D., Xu, D., Chai, X., & Ge, M. (2025). Characteristics of the blood–brain barrier in pediatric brain tumors. *Frontiers in Pediatrics*, 13, 1646641. <https://doi.org/10.3389/fped.2025.1646641>
- Haumann, R., Videira, J. C., Kaspers, G. J. L., et al. (2020). Overview of current drug delivery methods across the blood–brain barrier for the treatment of primary brain tumors. *CNS Drugs*, 34, 1121–1131. <https://doi.org/10.1007/s40263-020-00766-w>
- Hsu, J.-F., Chu, S.-M., Liao, C.-C., Wang, C.-J., Wang, Y.-S., Lai, M.-Y., Wang, H.-C., Huang, H.-R., & Tsai, M.-H. (2021). Nanotechnology and Nanocarrier-Based Drug Delivery as the Potential Therapeutic Strategy for Glioblastoma Multiforme: An Update. *Cancers*, 13(2), 195. <https://doi.org/10.3390/cancers13020195>
- Kuo, C.-F., & Majd, S. (2020). An improved in vitro blood–brain barrier model for applications in therapeutics' delivery to the brain. *Proceedings of the 42nd Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC)* (pp. 3331–3334). IEEE. <https://doi.org/10.1109/EMBC44109.2020.9175888>

FALL 2026

- Malik, J. R., Podany, A. T., Khan, P., Shaffer, C. L., Siddiqui, J. A., Baranowska-Kortylewicz, J., Le, J., Fletcher, C. V., Ether, S. A., & Avedissian, S. N. (2023). Chemotherapy in pediatric brain tumor and the challenge of the blood–brain barrier. *Cancer Medicine*, 12(23), 21075–21096. <https://doi.org/10.1002/cam4.6647>
- Martinez, P. J., Green, A. L., & Borden, M. A. (2024). Targeting diffuse midline gliomas: The promise of focused ultrasound-mediated blood–brain barrier opening. *Journal of Controlled Release*. <https://doi.org/10.1016/j.jconrel.2023.11.037>
- Miguel Llordes, G., Medina Pérez, V. M., Curto Simón, B., Castells-Yus, I., Vázquez Sufuentes, S., & Schuhmacher, A. J. (2023). Epidemiology, diagnostic strategies, and therapeutic advances in diffuse midline glioma. *Journal of Clinical Medicine*, 12(16), 5261. <https://doi.org/10.3390/jcm12165261>
- Morris, E. K., Daignault-Mill, S., Stehbens, S. J., Genovesi, L. A., & Lagendijk, A. K. (2023). Addressing blood–brain tumor barrier heterogeneity in pediatric brain tumors with innovative preclinical models. *Frontiers in Oncology*, 13, 1101522. <https://doi.org/10.3389/fonc.2023.1101522>
- National Brain Tumor Society. (2026, March 6). *Brain tumor facts*. <https://braintumor.org/brain-tumors/about-brain-tumors/brain-tumor-facts/>
- Omidian, H., & Mfofo, K. (2023). Exploring the Potential of Nanotechnology in Pediatric Healthcare: Advances, Challenges, and Future Directions. *Pharmaceutics*, 15(6), 1583. <https://doi.org/10.3390/pharmaceutics15061583>
- Rahman, R., Janowski, M., Killick-Cole, C. L., Campbell, E. W., Walczak, P., Khatua, S., Faltings, L., Symons, M., Schneider, J. R., Kwan, K., Boockvar, J. A., Gill, S. S., Oliveira, J. M., Beccaria, K., Carpentier, A., Canney, M., Pearl, M., Veal, G. J., & Meijer, L. (2023). Childhood brain tumors: A review of strategies to translate CNS drug delivery to clinical trials. *Cancers*, 15(3), 857. <https://doi.org/10.3390/cancers15030857>
- Rechberger, J. S., Toll, S. A., Biswas, S., You, H. B., Chow, W. D., Kendall, N., Navalkele, P., & Khatua, S. (2025). Advances in the repurposing and blood–brain barrier penetrance of drugs in pediatric brain tumors. *Cancers*, 17(3), 439. <https://doi.org/10.3390/cancers17030439>

- Shah, N., Sohl, J., Ganassi, M., Guglielmi, L., & Badodi, S. (2025). Challenges and innovations in paediatric brain tumour treatments. *Pharmaceutics*, 17(12), 1561. <https://doi.org/10.3390/pharmaceutics17121561>
- Si, J., Liu, Z., Gu, F., Jin, X., & Ma, Y. (2025). Nanoparticle-based delivery systems for targeted therapy in brain tumors: Progress, challenges and perspectives (Review). *International Journal of Oncology*, 67, 83. <https://doi.org/10.3892/ijo.2025.5789>
- Suter, R. K., Rodriguez-Blanco, J., & Ayad, N. G. (2020). Epigenetic pathways and plasticity in brain tumors. *Neurobiology of Disease*, 145, 105060. <https://doi.org/10.1016/j.nbd.2020.105060>
- Thavarajasingam, S. G., Kilgallon, J. L., Ramsay, D. S. C., et al. (2023). Methodological and ethical challenges in the use of focused ultrasound for blood–brain barrier disruption in neuro-oncology. *Acta Neurochirurgica*, 165, 4259–4277. <https://doi.org/10.1007/s00701-023-05782-5>
- Vodilovska, V., Ackovska, N., & Ivanoska, I. (2025). Leveraging graph attention networks for blood–brain barrier permeation prediction. In *Proceedings of the 48th MIPRO ICT and Electronics Convention* (pp. 168–173). IEEE. <https://doi.org/10.1109/MIPRO65660.2025.11131888>
- Vanbilloen, W. J. F., Rechberger, J. S., Anderson, J. B., Nonnenbroich, L. F., Zhang, L., & Daniels, D. J. (2023). Nanoparticle Strategies to Improve the Delivery of Anticancer Drugs across the Blood–Brain Barrier to Treat Brain Tumors. *Pharmaceutics*, 15(7), 1804. <https://doi.org/10.3390/pharmaceutics15071804>
- Yang, S., Wallach, M., Krishna, A., Kurmasheva, R., & Sridhar, S. (2021). Recent Developments in Nanomedicine for Pediatric Cancer. *Journal of Clinical Medicine*, 10(7), 1437. <https://doi.org/10.3390/jcm10071437>