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CASE REPORT

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Synergistic antitumor effect of temozolomide and perampanel in pediatric glioma: a case report and in vitro validation using patient-derived glioma sphere cells

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Abstract

Pediatric low-grade gliomas are the most common central nervous system tumors; however, therapeutic options remain limited for tumors involving critical structures, such as the optic pathway, particularly when malignant transformation occurs. Temozolomide is widely used to treat high-grade gliomas; however, its clinical benefits in pediatric low-grade gliomas have been inconsistent. Recent laboratory studies have suggested that the antiepileptic drug perampanel, a selective noncompetitive antagonist of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)-type glutamate receptor, may enhance the antitumor activity of temozolomide; however, this has not been demonstrated in patients. To the best of our knowledge, this is the first clinical case in which a child with recurrent treatment-refractory optic pathway glioma with malignant transformation exhibited marked radiographic tumor regression following treatment with a combination of temozolomide and perampanel. This unexpected clinical response prompted further investigation using patient-derived glioma sphere cells generated from two independent glioma cases. In vitro analyses showed that perampanel suppressed cell proliferation and exhibited synergistic cytotoxicity when combined with temozolomide. Immunofluorescence analysis of the patient's tumor tissue revealed high expression of GRIA1-4, a gene encoding the AMPA receptor subunit, particularly within CD44-positive glioma stem-like cells, supporting a mechanistic association between AMPA receptor signaling and treatment sensitivity. Complementary transcriptomic analysis using publicly available datasets showed that the elevated expression of GRIA family genes was associated with favorable survival in low-grade gliomas. Taken together, these findings suggest that perampanel potentiates the antitumor effects of temozolomide and highlight GRIA expression as a potential biomarker for AMPA receptor–targeted strategies in glioma.

Keywords Glioma, Temozolomide, Perampanel, AMPA receptors, GRIA, Patient-derived glioma sphere cells

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Introduction

Pediatric low-grade gliomas (LGGs) are the most common central nervous system tumors in children [1]. Although their prognosis is generally favorable compared to that of high-grade gliomas, tumors involving critical structures such as the optic pathway are often associated with significant morbidity and limited therapeutic options [2]. Standard chemotherapy, represented by the vincristine and carboplatin regimen introduced by Packer et al., has remained largely unchanged for decades, and recurrence or progression is frequently observed [3]. Novel molecular targeted therapies, including BRAF and MEK inhibitors, have shown promise in select cases; however, access, approval, and efficacy remain variable across regions [4].

Recent in vitro studies have demonstrated that perampanel (PER), a selective, noncompetitive AMPA receptor antagonist approved for epilepsy, enhances the antitumor activity of temozolomide (TMZ) in glioma cell lines [5, 6]. However, the clinical utility of PER in glioma therapy has not been reported [7].

Here, we describe what is, to our knowledge, the first case of a patient with recurrent, treatment-refractory LGG with malignant transformation who exhibited marked radiographic tumor regression after receiving combination therapy with TMZ and PER. We further substantiate this observation through in vitro experiments using patient-derived glioma sphere cells (GSCs), confirming the synergistic antitumor effects of this therapeutic combination.

Case presentation

A 16-year-old boy with a history of an optic pathway glioma presented with worsening seizures. At the age of 2, he developed macrocephaly and hydrocephalus, which prompted further evaluation. Magnetic resonance imaging (MRI) revealed an optic pathway tumor involving the optic chiasm and hypothalamus. Partial resection was performed, and histopathology confirmed a pilocytic astrocytoma with a Ki-67 index of approximately 1%. Postoperatively, adjuvant chemotherapy with vincristine and carboplatin was administered, resulting in temporary disease control for approximately nine years. At 9 years of age, the patient experienced generalized seizures. Electroencephalography revealed epileptiform discharges localized in the parietal region. He was diagnosed with symptomatic epilepsy, and valproic acid and levetiracetam were administered, which successfully controlled the seizures. Follow-up MRI revealed no evidence of tumor progression. At 11 years of age, follow-up imaging revealed a local recurrence in the left thalamic region. A second resection was performed, and histopathological examination showed increased proliferative activity with a Ki-67 index of approximately 10% (Fig. 1a, b).

Weekly vinblastine and focal proton beam therapy were administered, resulting in temporary disease stabilization. At age 14 years, MRI demonstrated leptomeningeal dissemination involving the frontal and temporal lobes and the perihippocampal region (Fig. 1e–h). Repeat biopsy revealed malignant transformation with prominent nuclear atypia and a Ki-67 index of approximately 30% (Fig. 1c, d). Genomic analysis identified a BRAF V600E mutation, but no alterations in MGMT, IDH1, IDH2, H3F3A, or HIST1H3B. Worsening seizures accompanied tumor progression, leading to the addition of PER; however, seizure control was not achieved. Despite the presence of the BRAF V600E mutation, BRAF/MEK inhibitors were not approved for pediatric use in Japan at the time, precluding targeted therapy. Vinblastine therapy was continued; however, the tumor response was minimal. Given the progressive treatment-refractory nature of the disease, a multidisciplinary discussion concluded with a shift towards palliative care. Since TMZ is an orally administered chemotherapy that offers outpatient treatment without the need for hospitalization or continuous infusions, we elected to initiate TMZ (days 1–5 of a 28-day cycle). Within several months of initiating TMZ treatment, the patient achieved complete resolution of the seizures. Six months later, MRI revealed a marked reduction in leptomeningeal disease burden (Fig. 1i–l). This unanticipated clinical improvement prompted us to hypothesize a potential synergistic antitumor interaction between TMZ and antiepileptic therapies.

To test this hypothesis, we conducted in vitro experiments using glioma sphere cells (GSCs) derived from two additional patients with high-grade gliomas, as cultures could not be established in the present case (see Supplementary Information). GSCs were treated with TMZ and three antiepileptic agents: valproic acid, levetiracetam, and PER. Of these, only PER significantly inhibited GSC proliferation, with a Ki of 63 ± 2 μM and a steep dose-response curve (Hill coefficient: 4.38 ± 0.35 on day 4) (Fig. 2a). Valproic acid and levetiracetam exhibited negligible effects (Fig. 2b, c), while TMZ alone demonstrated moderate inhibition (Ki = 33 ± 5 μM; Hill coefficient = 1.72 ± 0.41) (Fig. 2d). Notably, co-treatment with TMZ and PER significantly enhanced the inhibition of cell viability compared with treatment with either agent alone ($p < 0.01$) (Fig. 2e, f), suggesting a synergistic effect. Given that PER acts as an AMPA receptor antagonist, we evaluated the expression of AMPA receptor subunits in these GSCs. Immunocytochemical analysis demonstrated expression of GRIA2 and GRIA4 in the GSCs, whereas GRIA1 and GRIA3 were not detected (Fig. 2g–l, Supplementary Fig. 1).

Immunofluorescence staining of the resected tumor samples revealed robust expression of the AMPA

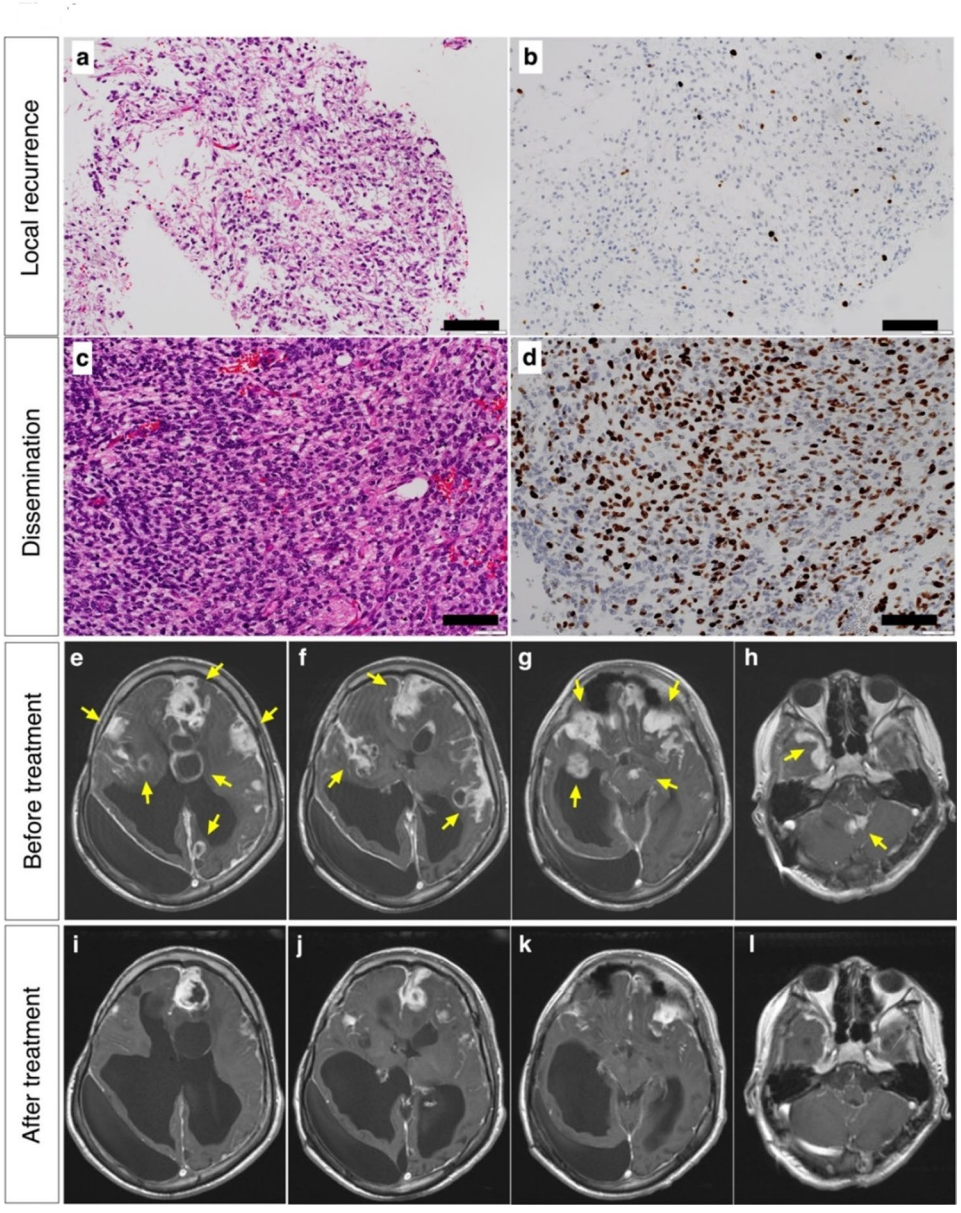

Fig. 1 Histopathological and radiological findings demonstrating malignant transformation and treatment response. Histopathological and radiological findings. The local recurrent tumor was diagnosed as a pilocytic astrocytoma on hematoxylin and eosin (H&E) staining (**a**), and Ki-67 staining revealed low proliferative activity (**b**) at 11 years of age. The disseminated tumor exhibited a markedly increased nuclear-to-cytoplasmic (N/C) ratio on hematoxylin and eosin staining (**c**), and Ki-67 staining revealed moderate to high proliferative activity (**d**) at 14 years of age. Scale bar = 100 µm. Axial contrast-enhanced magnetic resonance imaging (MRI) performed before TMZ initiation shows extensive leptomeningeal dissemination of the tumor with prominent contrast enhancement in the frontal lobe, temporal lobe, and perihippocampal regions (**e**–**h**: arrows). MRI performed six months after the initiation of TMZ demonstrated marked tumor regression (**i**–**l**)

receptor subunits GRIA1–4 (Fig. 3a, e, i, m). To further examine GRIA1-4 expression within the tumor regions, a spatial single-cell analysis was performed (Fig. 3q–t)[21]. Subsequent quadrant analyses of the integrated single-cell data highlighted the distinct enrichment of GRIA1-4 within the CD44-positive compartment (Fig. 3u). Remarkably, across the three tumor ROIs per marker, GRIA expression was consistently higher in CD44-positive cells than in CD44-negative cells (Fig. 3v); this difference was statistically confirmed by pooled analyses (Fig. 3w). In contrast, ABAT, a molecular target of valproic acid, was weakly expressed, whereas SV2A, a target of levetiracetam, was detected (Supplementary Fig. 2).

The relationship between receptor expression and prognosis was analyzed using pediatric datasets from the TARGET and St. Jude cohorts on the cBioPortal platform (https://www.cbioportal.org/). In pediatric low-gr ade gliomas (LGG), higher expression of GRIA1–4 was

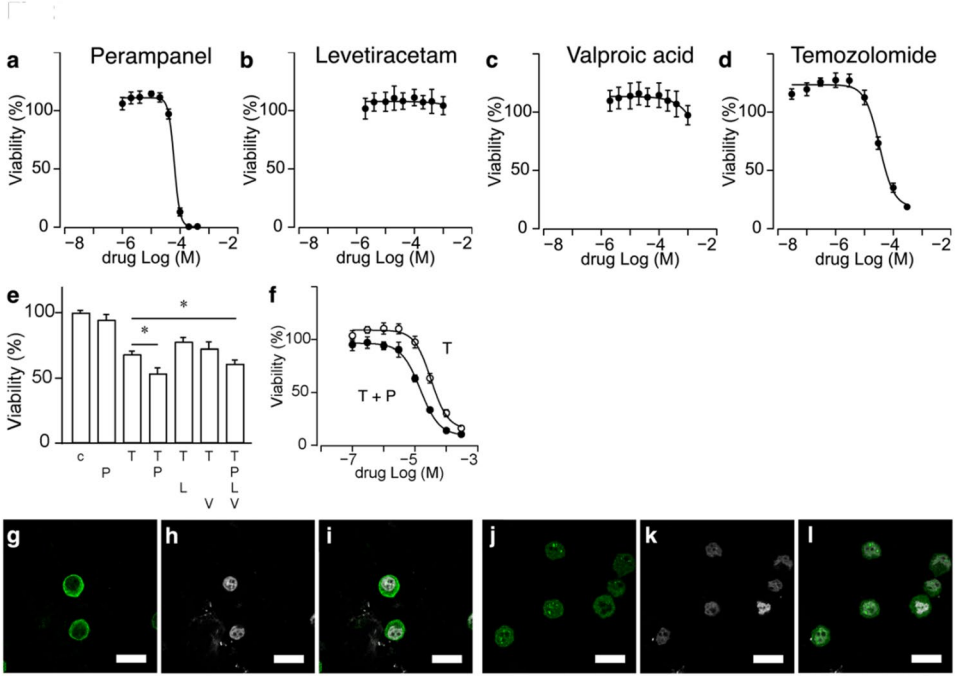

Fig. 2 In vitro synergistic effects of TMZ and PER and GRIA2/4 expression in patient-derived glioma cells. **a**: Proliferation assay of 30R cells treated with PER. The solid curve represents the nonlinear regression fit to the Hill equation, which estimated the inhibitory constant (Ki) and Hill coefficient as 63 ± 2 μM and 4.38 ± 0.35, respectively (n = 6). **b**: 30R cells treated with levetiracetam (n = 6). **c**: 30R cells treated with valproic acid (n = 6). **d**: 30R cells treated with TMZ. The solid curve is the fit by the Hill equation, which estimated Ki and Hill coefficient as 33 ± 5 μM and 1.72 ± 0.41, respectively (n = 6). **e**: Cell proliferation assay of 30R cells after treatment with various drugs for 4 days (n = 6). Treatments and their respective concentrations are as follows: c (control); P (PER at 40 μM); T (TMZ at 30 μM); L (levetiracetam at 1 mM); and V (valproic acid at 1 mM). *$p < 0.01$. **f**: Cell proliferation assay of 30R cells treated with TMZ alone (open circles) or in combination with 40 μM PER (closed circles). Solid curves represent fits to the Hill equation, yielding an estimated Ki of 33 ± 4 μM and a Hill coefficient of 1.63 ± 0.29 for TMZ alone, and a Ki of 15 ± 1 μM and a Hill coefficient of 1.44 ± 0.11 for the combination treatment (n = 6). **g**: GRIA2 (AMPA receptor) staining using an anti-GRIA2 antibody (1:200, clone 7G6, sc-517265; Santa Cruz Biotechnology) in glioma sphere cells (GSCs). **h**: Nuclei staining with 4′,6-diamidino-2-phenylindole (DAPI). **i**: Merged images of g and h. **j**: GRIA4 staining (1:100, clone F-9, sc-271894; Santa Cruz Biotechnology). **k**: Nuclei staining. **l**: Merged image of **j** and k. Bars = 20 μm

significantly associated with favorable overall survival compared with lower expression groups (Fig. 4a–d). In pediatric high-grade gliomas (HGG), elevated expression of GRIA1 and GRIA3 correlated with significantly better overall survival. However, GRIA4 showed an inverse association, with lower expression associated with better survival (Fig. 4g–j). For comparison, ABAT and SV2A, targets of valproic acid and levetiracetam, respectively, were associated with favorable survival in pediatric LGG when highly expressed (Fig. 4e, f). In contrast, no significant prognostic association was observed in pediatric HGG (Fig. 4k, l). Analysis of adult glioma datasets revealed partially overlapping patterns. In adult LGG, GRIA3 expression was associated with overall survival, whereas in adult HGG, both GRIA3 and GRIA4 expression levels were significantly associated with prognosis (Supplementary Fig. 3).

Discussion

This case provides the first clinical evidence suggesting that the combination of TMZ and PER exerts a synergistic antitumor effect on gliomas. The patient, whose tumor underwent malignant transformation and demonstrated resistance to multiple prior therapies, exhibited an unexpectedly robust clinical and radiographic response shortly after the introduction of PER in combination with TMZ. Although TMZ remains a cornerstone therapy for adult high-grade gliomas, its efficacy in pediatric gliomas—particularly in low-grade or high-risk subsets—has been inconsistent and remains far from established, with several clinical studies reporting only modest or variable benefit [8–11]. Therefore, the striking response in this case exceeded what would typically be expected from TMZ monotherapy. In vitro studies further substantiated this observation, as patient-derived glioma sphere cells (GSCs) demonstrated significantly enhanced cytotoxicity with the TMZ–PER combination compared with either agent alone, providing biological plausibility for the clinical effect. Collectively, these findings are the first to translate the previously described TMZ–PER synergy from in vitro models into a clinical context and underscore the potential therapeutic relevance of AMPA receptor antagonism in overcoming TMZ resistance.

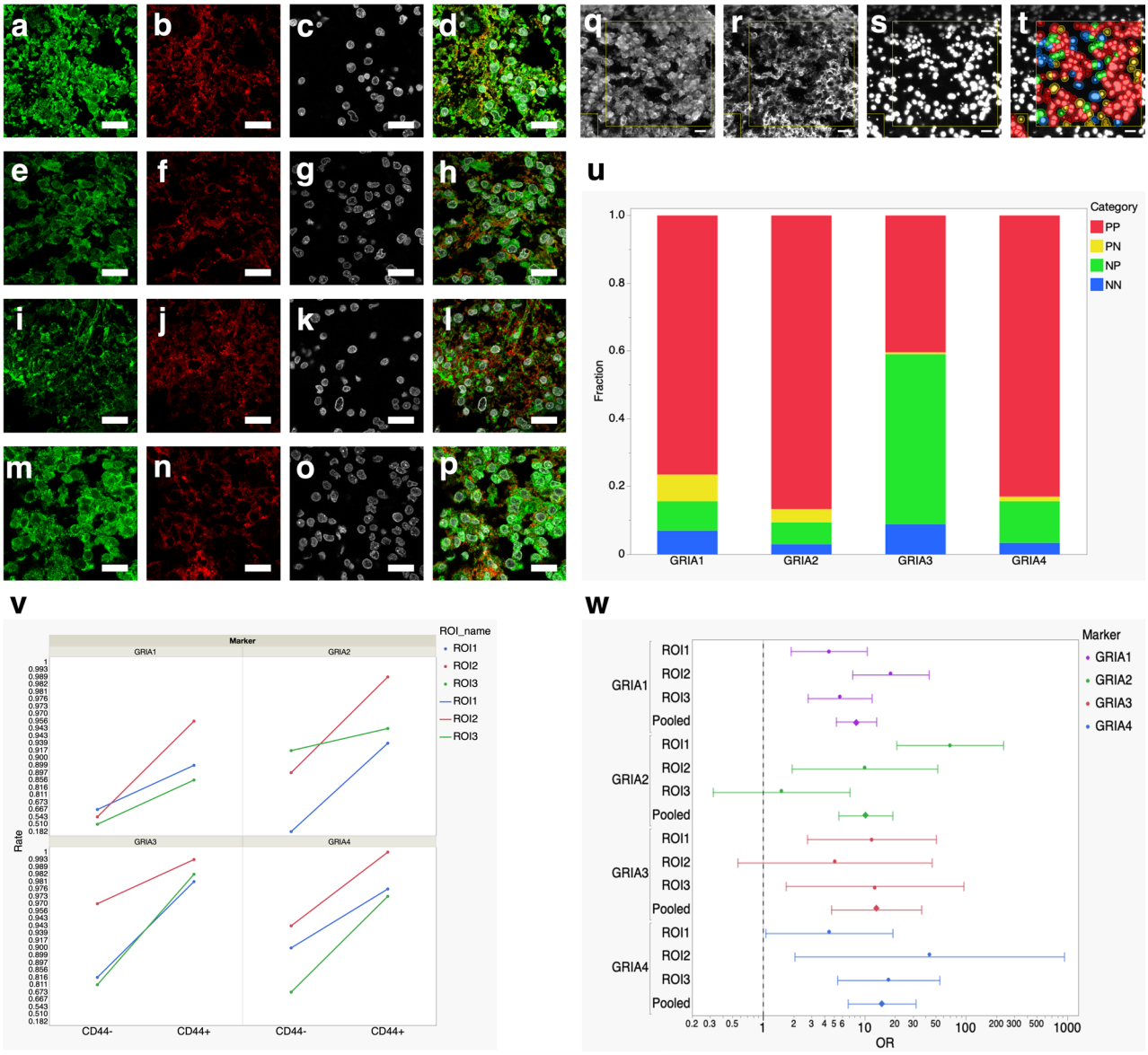

Fig. 3 Spatial single-cell analysis reveals enriched expression of the AMPA receptor subunits in a CD44-positive tumor cell compartment using a specimen resected at 14 years of age. **a**: Immunofluorescence staining showing GRIA1 expression in a specimen resected at 14 years of age. **b**: Immunofluorescent staining for CD44 in the same specimen. c: Nuclei staining with 4′,6-diamidino-2-phenylindole (DAPI). d: Merged image combining a, b, and c. e: GRIA2 staining. **f**: CD44 staining. **g**: Nuclei staining. **h**: Merged image of e, f, and g. **i**: GRIA3 staining. **j**: CD44 staining. **k**: Nuclei staining. **l**: Merged image of i, j, and k. **m**: GRIA4 staining. **n**: CD44 staining. **o**: Nuclei staining. **p**: Merged image of m, n, and o. Scale bar = 20 µm. **q**–**s**: Representative multiplex immunofluorescence images of glioma tissues stained for GRIA1 (**q**), CD44 (**r**), and DAPI (**s**) captured using a whole-slide scanner. Scale bar = 20 µm. **t**: Visualization of segmented cells categorized by CD44 and GRIA1 expression status. Red: CD44+/GRIA1+ (PP); Yellow: CD44+/GRIA1- (PN); Green: CD44-/GRIA1+ (NP); Blue: CD44-/GRIA1- (NN). Scale bar = 20 µm. **u**: Stacked bar charts for each GRIA subunit (GRIA1-4) illustrating the relative proportions of the four cell phenotypes (PP, PN, NP, and NN) across the annotated regions of interest (ROIs), grouped by CD44 and GRIA status. **v**: Paired slope plots comparing the proportions of GRIA1-4 positive cells between CD44-positive (CD44+) and CD44-negative (CD44-) cells within matched ROIs (ROI1-3). **w**: Forest plots summarizing the odds ratios (ORs) and 95% confidence intervals for the likelihood of GRIA1-4 expression in relation to CD44 positivity. For each GRIA subunit, a pooled estimate was included to represent the overall odds ratio combined across all evaluated ROIs

The relevance of this synergy is underscored by a growing body of literature implicating glutamatergic signaling as a central driver of glioma progression. Glutamate released by glioma cells engages AMPA-type glutamate receptors to promote depolarization, calcium influx, proliferation, invasion, and resistance to apoptosis [12–14]. Glioma–neuron synaptic structures mediated by AMPA receptors have recently been recognized as key facilitators of tumor growth and malignant behavior [15]. These findings provide a strong rationale for targeting glutamate signaling as a therapeutic strategy. PER, a selective noncompetitive AMPA receptor antagonist approved for

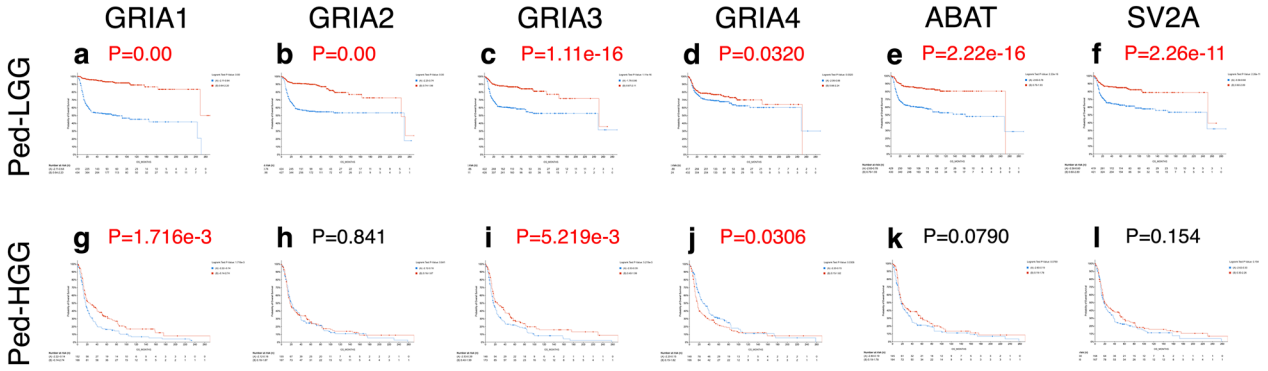

Fig. 4 Survival analysis of pediatric low-grade glioma (LGG) and high-grade glioma (HGG) stratified by receptor-associated gene expression. Kaplan–Meier overall survival curves for pediatric glioma cohorts stratified by high versus low gene expression. **a**–**f**: Pediatric LGG. High expression of GRIA1, GRIA2, GRIA3, GRIA4, ABAT, and SV2A (red lines) was associated with better overall survival compared with low-expression groups (blue lines). **g**–**l**: Pediatric HGG. High expression of GRIA1 and GRIA3 (red lines) was associated with favorable overall survival (**g**, **i**), whereas low GRIA4 expression (blue line) correlated with better survival (**j**). No significant survival differences were observed for GRIA2, ABAT, or SV2A (**h**, **k**, **l**). *P*-values were calculated using the log-rank test

epilepsy, is, therefore, biologically well-positioned for repurposing in neuro-oncology.

Preclinical studies have demonstrated that PER not only reduces proliferation and induces apoptosis in glioma cell lines, but also potentiates the cytotoxic effects of TMZ. Salmaggi et al. and Tatsuoka et al. independently reported a clear synergy between the two agents, although responsiveness varied among cell lines, suggesting an underlying molecular heterogeneity that defines sensitivity [5, 6]. Our GSC-based analyses closely aligned with these findings. Because patient-derived GSCs retain patient-specific molecular features, our results provide mechanistic support that is more relevant to real-world tumor biology than immortalized cell lines alone [16]. However, we did not perform GRIA2 knockdown or other loss-of-function experiments, nor did we establish TMZ-resistant glioma models to determine whether disrupting AMPA receptor signaling directly reduces TMZ resistance. Therefore, our findings should be interpreted as supporting an association between GRIA expression and sensitivity to TMZ–PER combination therapy, rather than as direct mechanistic evidence that GRIA2 or AMPA receptor signaling mediates TMZ resistance.

An important insight emerging from this case is the potential significance of the GRIA genes, which encode AMPA receptor subunits. The AMPA receptor consists of four subunits (GRIA1–4). In this patient's tumor, GRIA2 expression was particularly enriched within CD44-positive glioma stem-like cell populations. High GRIA expression may indicate greater dependence on glutamatergic signaling and, in turn, heightened vulnerability to AMPA receptor blockade. Furthermore, our transcriptomic analysis of publicly available datasets demonstrated that elevated GRIA1-4 expression correlated with better overall survival in glioma, underscoring the biological relevance of GRIA genes in tumor behavior. To the best of our knowledge, this study is the first to highlight the clinical and biological relationship between GRIA expression and gliomas, suggesting that GRIA may serve as both a predictive biomarker for AMPA receptor–targeted therapy and a prognostic marker. Collectively, these findings support the development of GRIA-based companion diagnostics that enable molecular stratification and personalized therapeutic strategies for gliomas. Importantly, GRIA2 (GluA2) is uniquely subject to RNA editing at the Q/R site, a post-transcriptional modification that critically regulates AMPA receptor calcium permeability. Incomplete Q/R site editing of GluA2 results in calcium-permeable AMPA receptors, which enhance cellular excitability and downstream proliferative signaling, and aberrant editing has been implicated in glioma biology and therapeutic responsiveness [17]. In addition, glioma cells can form bona fide AMPA receptor-dependent neuron-glioma synapses, enabling electrical and synaptic integration into neural circuits and promoting tumor progression [15]. This synaptic integration enhances activity-dependent depolarization and calcium influx, thereby driving proliferation. Although we observed strong GRIA2 protein enrichment within CD44-positive tumor cells, we did not assess the GRIA2 RNA editing status or electrophysiological synaptic integration in this case. These mechanistic features may further refine our understanding of AMPA receptor-mediated therapeutic vulnerability and warrant further investigation.

In addition to the canonical AMPA blockade, other mechanisms may contribute to the observed therapeutic effects of PER. PER modulates neuronal excitability through AMPA-independent electrophysiological actions, including its effects on voltage-gated sodium and M-type potassium currents [18]. Moreover, it is conceivable that PER may influence intracellular drug handling by altering drug retention or efflux dynamics, potentially

enhancing the activity of concomitant agents such as TMZ. Although these possibilities were not directly examined in the present study, they may help explain the observed cooperative antiproliferative effects and warrant exploration in future mechanistic studies.

The translational implications of the present study are noteworthy. PER is widely used in children with epilepsy and has a well-established safety profile and favorable pharmacokinetics, including excellent blood–brain barrier penetration [19, 20]. Thus, it is an attractive candidate for rapid clinical translation without the developmental constraints of novel therapeutics. The combined use with TMZ may be particularly promising for tumors that exhibit resistance to standard therapies. Importantly, our findings should not be interpreted as supporting TMZ as a standard first-line therapy for pediatric low-grade gliomas because its clinical benefit remains limited. Rather, this combination may warrant further investigation in more aggressive clinical settings, such as in high-grade glioma or low-grade glioma with malignant transformation or treatment-refractory progression. In addition, the dual action of PER, antiepileptic, and antitumor agents provides added clinical value in gliomas, where seizures are common and contribute substantially to morbidity.

Nonetheless, this study has several limitations. Although the clinical response in this patient was striking, this study describes a single case and causality cannot be firmly established. Biological features unique to the tumor may have contributed to the observed sensitivity. Although our in vitro analyses demonstrated a clear synergy between TMZ and PER, the GSC models used were derived from only two glioma cases. In addition, we were unable to include a GRIA-low GSC model as a negative control to evaluate the specificity of PER sensitivity. Validation across a larger and more molecularly diverse panel of patient-derived GSCs is essential to determine whether the synergistic effects observed in this study represent a broadly applicable therapeutic mechanism. Furthermore, although GRIA expression has emerged as a compelling candidate biomarker, this finding requires prospective validation in larger patient cohorts and functional studies before it can be integrated into clinical decision-making processes.

Conclusion

In summary, this case highlights AMPA antagonism as a promising adjunct to alkylating chemotherapy for gliomas. The combined clinical response and patient-derived experimental data suggest that glutamatergic signaling may represent a therapeutically exploitable vulnerability in selected tumors. Further mechanistic studies and prospective clinical evaluations of PER are required to determine its broader applicability.

Abbreviations

AMPA	Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
GSCs	Glioma sphere cells
LGGs	Low-grade gliomas
MRI	Magnetic resonance imaging
PER	Perampanel
TMZ	Temozolomide
TCGA	The cancer genome atlas

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40478-026-02297-9.

Supplementary Material 1

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Author contributions

All the authors contributed to the conception and design of this study. TO, MH, CO, and NA performed material preparation, data collection, and analysis. TO wrote the first draft of the manuscript, and all authors commented on the previous versions of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

All procedures involving human tissues were approved by the Institutional Review Board of Kansai Medical University (approval number: 2017188; March 14, 2023). Written informed consent was obtained from all the participants, their parents, and their legal guardians.

Consent for publication

Patients signed informed consent regarding publishing their data and photographs.

Competing interests

The authors declare no competing interests.

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