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Immune Pathway Gene (Cxcl8) And Glutamate Signalling Gene (Slc17a7) Expression in Glioma-Related Seizures: A Pilot Study

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Abstract

Background and Objectives: Glial neoplasms account for approximately 50% of adult primary brain tumors. Seizures are a common manifestation, affecting nearly 90% of low-grade and 50% of high-grade glioma patients. Of these, around 30% remain drug-resistant despite surgical resection. The mechanisms underlying glioma-associated seizures are complex and not fully elucidated. Emerging evidence points toward multifactorial origins involving genomic, transcriptomic, proteomic, and metabolomic dysregulation. Notably, the glutamate signalling and immune modulation pathways have been implicated. This study aimed to investigate the mRNA expression of SLC17A7 (glutamate signalling) and CXCL8 (immune trafficking) genes in intraoperative tumor tissue of glioma patients with a particular focus on the potential differences between patients who experience seizures and those who do not.

Methods: In this prospective study, 50 glioma patients were enrolled, 25 with seizures and 25 without. Patients with recurrent tumors or non-tumor-related seizures were excluded. Following preoperative assessments and surgical intervention, intraoperative tumor tissue samples were collected. mRNA expression of SLC17A7 and CXCL8 was analysed using RT-PCR. All ethical standards were adhered to, and the genetic analysis team was blinded to clinical seizure status.

Results: CXCL8 downregulation was observed in 64% of glioma patients with seizures, compared to 44% without seizures. Although the difference was not statistically significant, this trend suggests a potential role for CXCL8 in the pathogenesis of seizures. SLC17A7 mRNA could not be reliably detected, despite repeated attempts. The likely cause is mRNA instability, possibly due to microRNA interference or alternative splicing.

Conclusions: CXCL8 downregulation appears more frequent in glioma patients with seizures, indicating a possible link to immune dysregulation in epileptogenesis. SLC17A7 mRNA was undetectable via RT-PCR, possibly due to its instability or alternative splicing in glioma tissue. Despite DNA-level amplification of SLC17A7 reported in other studies, this may not translate to increased mRNA or protein expression. Further mRNA expression studies in larger cohorts are needed to validate these findings.

Keywords: Glioma, seizures, SLC17A7, CXCL8, glutamate pathway, Immune trafficking

Introduction

Glial neoplasms constitute nearly 50% of adult primary brain tumors, with seizures affecting up to 90% of low-grade and 50% of high-grade glioma cases.[1] About 30% remain drug-resistant even after resection.[2] Seizures, often the first symptom, can be focal or generalized and significantly impair quality of life.[3] Unlike other focal epilepsies, glioma-related seizures have distinct, often refractory mechanisms. Their occurrence varies with tumor type and location-more common in frontal and temporal lobes-but this is not always predictable, raising key questions about seizure susceptibility and resistance.

Seizure etiology in glioma is complex and not fully understood. Before the occurrence of the first spontaneous seizure, several pathological changes occur in the brain tissue (including

neurons and glia), such as reactive gliosis and blood-brain barrier compromise. These changes ultimately lead to a state of hyperexcitability, which is associated with a low seizure threshold.[4] While the exact pathophysiological mechanisms remain unclear, seizures in brain tumor patients are thought to arise from factors like mechanical compression, altered vascularization and oxygen supply, inflammation, and imbalances in neurotransmitters (especially GABA and glutamate).[5]

Current evidence suggests that the etiology is multifactorial, involving alterations at the genomic, transcriptomic, epigenomic, proteomic, and metabolomic levels.[6] Among these, glutamate pathway activation and disruption of immune pathway has garnered the most attention.[7] Evidence also suggests that growth of tumor stimulates seizures, which in turn encourages tumor growth, suggesting that the two conditions may share common pathogenesis.[8-10] Elevated glutamate levels have been observed in the tumour microenvironment, possibly due to increased expression of glutamate transporters[11], contributing to seizures as well as tumour development. In this study, we investigated the mRNA expression of genes involved in the glutamate signaling pathway (SLC17A7) and the immune trafficking pathway (CXCL8) in the tumor tissue of patients diagnosed with glioma, with a particular focus on the potential differences between those who experience seizures and those who do not.

To the best of our knowledge, no comparative studies from Indian literature have examined gene expression differences between glioma patients with and without seizures. Internationally, only one study[12] has investigated this using gene sequencing, rather than mRNA expression, in intraoperative human glioma tissue. This is the first study to specifically evaluate mRNA expression of the CXCL8 gene in intraoperative glioma samples. This study could provide a better understanding of molecular mechanisms underlying glioma-associated epilepsy and potentially identify biomarkers for prognosis or therapeutic targeting.

Methods

This prospective observational, single-blinded study was conducted over 18 months involved glioma patients operated at our institution, aiming to assess mRNA expression levels of SLC17A7 and CXCL8 as the primary outcome measure. Inclusion criteria encompassed glioma patients with or without a history of seizures across all age groups, while patients with recurrent glioma or seizures due to metabolic or other non-tumor causes were excluded.

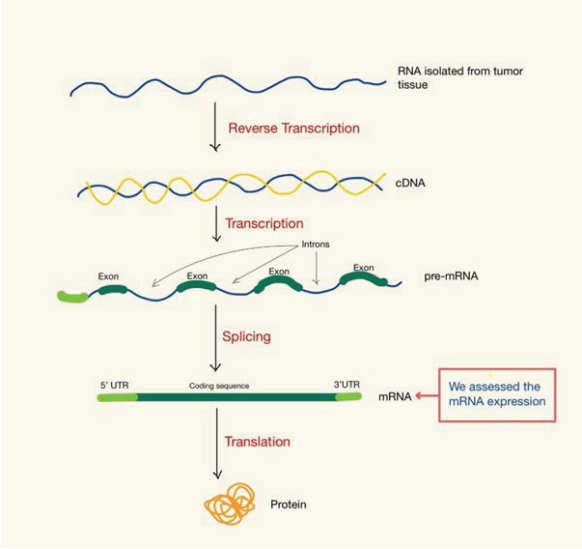


Figure 1: Schematic diagram of the process. RNA was isolated from glioma tissue. Complementary DNA (cDNA) was synthesized from the RNA using reverse transcription. Gene expression levels (upregulation or downregulation) were assessed by analysing the quantity of mRNA transcripts present, serving as a proxy for gene activity.

A procedure overview has been provided in Figure 1. Preoperative evaluation included seizure history, neurological assessment, and imaging (CT and MRI), followed by surgery with subsequent histopathology and gene expression studies. Tumour samples were analysed for mRNA expression of SLC17A7 and CXCL8, comparing glioma patients with seizures (on antiepileptic drugs) and those without seizures (not on antiepileptic drugs). Gene expression was assessed qualitatively; to compare the relative upregulation or downregulation of the SLC17A7 and CXCL8 genes between tumor and peritumoral samples, and the genetic analysis team was blinded to the seizure status.

Procedure- Informed consent was obtained from all patients after the procedure was explained in their native language. During surgery, the tumor and peritumour tissues were collected. Tumor samples were preserved in Phosphate Buffered Saline (PBS) at -80°C for DNA isolation and in RNA later at -80°C for RNA isolation, using kit-based methods. For RNA isolation, tissue was homogenized in 1 mL of Trizol and incubated at room temperature for 10 minutes, followed by standard RNA extraction procedures, including quality check via 1.2% gel electrophoresis. Complementary DNA (cDNA) was synthesized using the Revert aid kit (Thermo Fisher Scientific) with a reaction mixture containing buffer, dNTPs, primers, reverse transcriptase, RNAse inhibitor, and 500 ng of RNA. PCR conditions included incubation at 25°C for 5 minutes, 42°C for 1 hour, 70°C for 5 minutes, and a hold at 4°C. GAPDH (housekeeping gene) was used to confirm cDNA synthesis, with quality checked on 2% gel electrophoresis. RT-qPCR was performed using SyBr Green, with separate master mixes prepared for SLC17A7, CXCL8, and GAPDH.

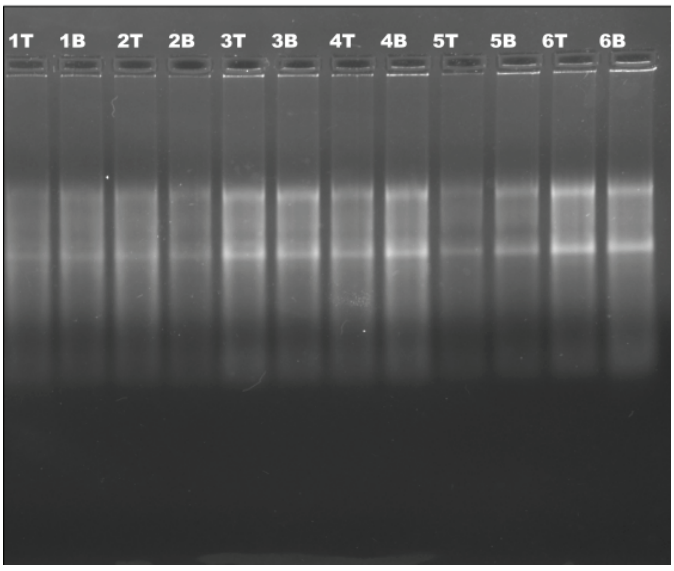


Figure 2a: 0.8% gel electrophoresis image showing RNA isolated. 1T, 2T, 3T, 4T, 5T, 6T- RNA from Tumor tissue of 1,2,3,4,5,6 patients. 1B,2B, 3B, 4B, 5B, 6B- RNA from peritumoral tissue of the same patients.

The forward and reverse primers used for CXCL8 were TTCTGCATCAGCTTTGGCATCC and GCCACAATAGCAAAGCCGAA respectively. The RT-qPCR reaction mixes included SyBr Green, primers, nuclease-free water, and diluted cDNA. PCR conditions were 95°C for 5 minutes, followed by cycles of 95°C for 30 seconds, 58°C for 30 seconds,

and a melt curve from 65°C to 95°C. The final PCR products were quality-checked using 2% gel electrophoresis (Figure 2). Figure 3 displays the RT-PCR amplification and melt curves for the gene.

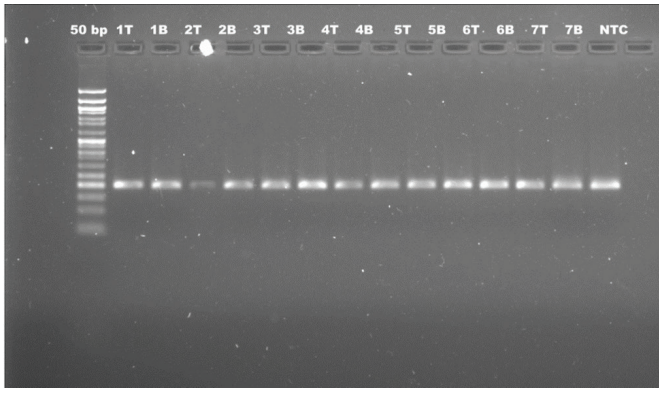


Figure 2b: 2% gel electrophoresis showing Complementary DNA (cDNA) isolated. 50bp- 50 base pairs ladder 1T, 2T, 3T, 4T, 5T, 6T, 7T- cDNA isolation from tumor tissue of 1,2,3,4,5,6,7 patients. 1B,2B, 3B, 4B, 5B, 6B, 7B- cDNA isolated from the peritumoral tissue of the same patients.

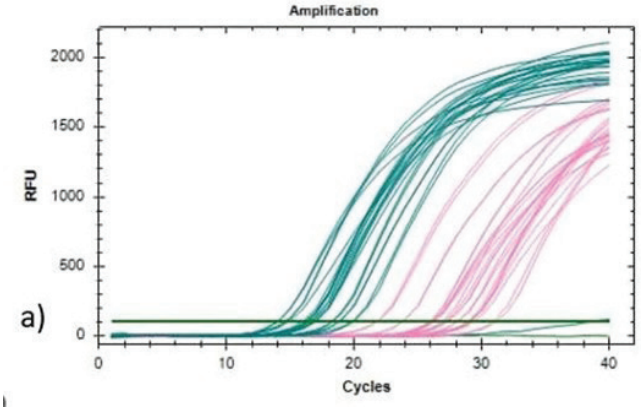


Figure 3a: Amplification curve of CXCL8 gene. A sigmoidal (S-shaped) curve indicating successful amplification of the target gene (CXCL8). Pink line represents amplification in tumor tissue, while green lines represent housekeeping gene (GADPH). In RT-PCR, curves for housekeeping genes appear in both amplification and melt curves because they are used as internal controls to normalize gene expression. Their stable expression ensures reliable comparison across samples.

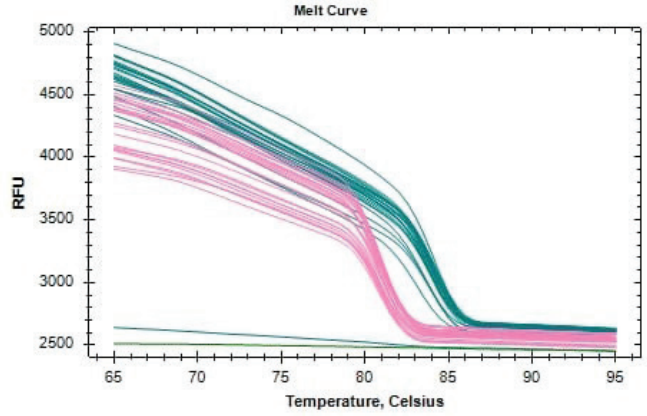


Figure 3b: The melt curve of the CXCL8 gene in RT-PCR shows how double-stranded DNA denatures with increasing temperature, helping confirm product specificity. In the RFU vs. temperature graph, the x-axis represents temperature (°C) and the y-axis shows fluorescence intensity. A sharp, single drop in RFU indicates a specific product, while a gradual or multi-step decline suggests non-specific amplification. In this case, the sharp drop confirms successful amplification of CXCL8. Pink line represents tumor tissue while green is housekeeping gene (GADPH).

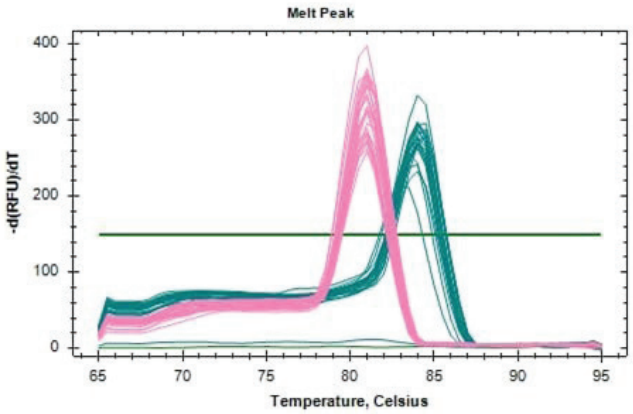


Figure 3c: Melt peak of CXCL8 gene. The melt curve is performed after the amplification cycles to check the specificity of the PCR product. A single, well-defined peak in the curve indicates that a single, specific PCR product (CXCL8) has been amplified. Pink line represents amplification in tumor tissue. Green lines represent housekeeping gene(GADPH).

Statistical analysis was performed using SPSS version 25.0, with categorical variables presented as numbers and percentages, and quantitative variables as mean ± SD or median with interquartile range. The Shapiro-Wilk test assessed data normality; non-parametric (Mann-Whitney) or parametric (Independent t-test) methods were used accordingly, and Chi-square or Fisher's exact test was applied for qualitative comparisons. A p-value < 0.05 was considered statistically significant.

Results

We examined the potential correlation between the mRNA expression of the glutamate pathway gene SLC17A7 and the immune trafficking pathway gene CXCL8 in glioma tissue in the context of glioma-associated epilepsy (Table 1).

Table 1: Comparison of CXCL8 between Glioma with and without seizure.

CXCL8	Glioma with seizure group(n=25)	Glioma without seizure group(n=25)	Total	P value
Down regulation	16 (64%)	11 (44%)	27 (54%)	0.256†
Up regulation	9 (36%)	14 (56%)	23 (46%)	
Total	25 (100%)	25 (100%)	50 (100%)	

† Chi square test

The observation that **CXCL8** downregulation occurred in 64% of patients in the glioma with seizures group, compared to 44% in the glioma without seizures group, may suggest a potential contributory role of **CXCL8** downregulation in seizure development, although the difference was not statistically significant..

The SLC17A7 gene, also known as solute carrier family 17 member 7 encodes a protein that functions as a vesicular glutamate transporter, commonly referred to as VGLUT1. It is primarily involved in the transport of the neurotransmitter glutamate into synaptic vesicles in the brain.[13]

We were unable to successfully isolate the mRNA of SLC17A7 despite multiple attempts (Figure 4, 5). A possible reason for the failure could be the presence of some microRNAs causing

instability in the SLC17A7 mRNA, potentially impairing its detection.

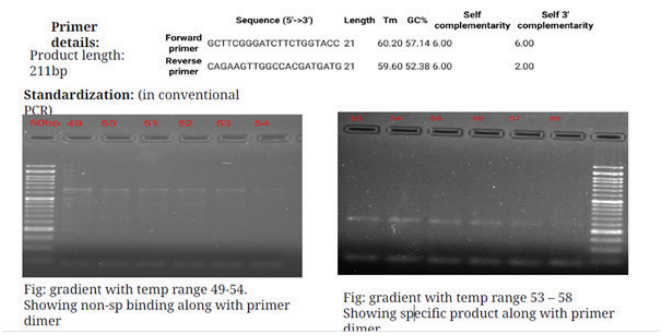
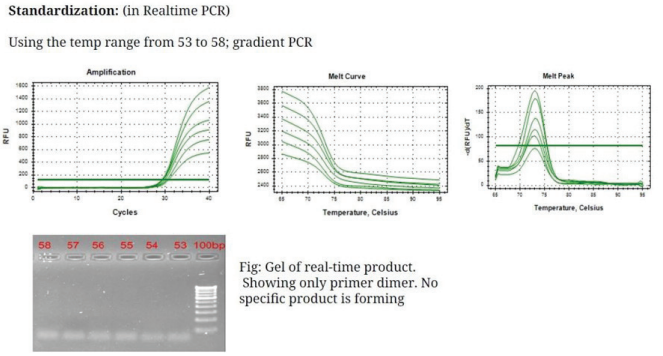


Figure 4: Initial attempts to isolate SLC17A7 mRNA using primers from the reference study.[12]

4a: Gel electrophoresis following gradient PCR at 49–54 °C and 53–58 °C shows only primer bands, with no specific product.



4b: Amplification and melt curves reveal expression of the housekeeping gene but not SLC17A7, confirming unsuccessful amplification of the target.

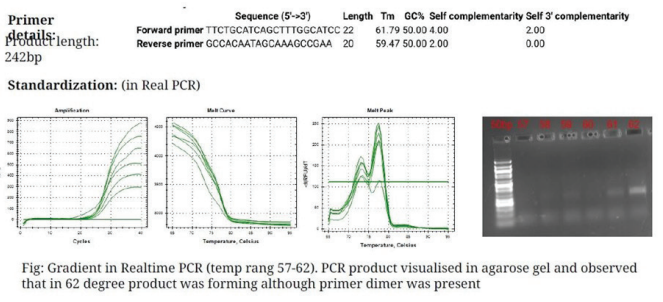
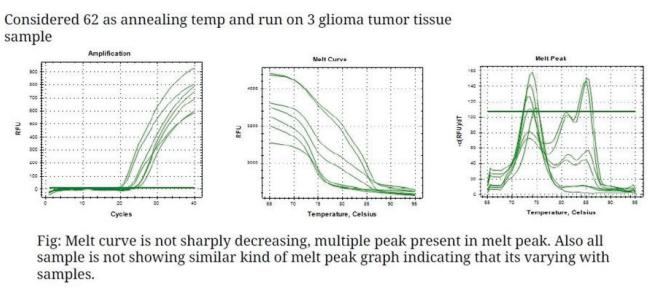


Figure 5: Further attempts to isolate SLC17A7 mRNA using a new primer designed by the biochemistry team.

5a: Gradient RT-PCR (57–62 °C) followed by agarose gel electrophoresis shows a faint product at 62 °C, although primer dimers are present.



5b: Amplification, melt, and melt peak curves display multiple melt peaks and lack of a sharp decrease in melt curve, with inconsistent patterns across samples, indicating non-specific amplification and failure to isolate a single target product.

Discussion

According to various sources, 30% to 80%[14-19] of patients with gliomas may experience seizures during the course of their disease or treatment. Current evidence suggests that the etiology is multifactorial, involving alterations at the genomic, transcriptomic, epigenomic, proteomic, and metabolomic levels.[20] The identification of effective therapeutic targets remains a major challenge and is the focus of ongoing investigation.

In this study, we examined the potential correlation between the mRNA expression of the glutamate pathway gene SLC17A7 and the immune trafficking pathway gene CXCL8 in glioma tumor tissue in the context of glioma-associated epilepsy.

Glioma-Associated Epilepsy: Correlation with SLC17A7 and CXCL8 Gene Expression

SLC17A7 gene: The SLC17A7 gene codes for a protein called vesicular glutamate transporter 1 (VGLUT1), also known as brain-specific sodium-dependent inorganic phosphate cotransporter. VGLUT1 is responsible for loading synaptic vesicles with glutamate and has been implicated in the regulation of quantal size and presynaptic plasticity.[20] The overexpression of VGLUT1 could represent a higher vesicular glutamate storage capacity, which may increase glutamatergic transmission and contribute to higher extracellular glutamate levels and excitability.[20] Glutamate levels were found to be elevated in tumors and adjacent tissues of epilepsy patients with high-grade gliomas, and in animal models with xenografted HGG.[21,22] Excess glutamate in the TME also encourages the polarization of pro-inflammatory tumor-associated macrophages to an anti-inflammatory state causing TME immunosuppression and facilitating tumor invasion. Moreover, neuroinflammatory pathways have been shown to have several points of intersection with glutamatergic signaling in the tumour microenvironment, further promoting both epileptogenesis and oncogenesis.7 Several Glutamate inhibitors like levetriacetam, ketamine, perampenel, mementine, and sulphasalzine have a role in controlling the growth of glioma and enhancing progression free survival.[23] Anticancer drug Temazolamide reduces frequency of seizures.[23] Future studies identifying pharmacotherapeutics targeting these elements is an extremely attractive therapeutic strategy for gliomas, for which very little therapeutic progress has been made in the past two decades.

The increased expression of the glutamate transporter may play an essential role in the pathogenesis of glioma related epilepsy.[24] Sontheimer et al.[25] found that treatment with sulfasalazine, a system Xc-specific blocker, can reduce the number of spontaneous epileptic events in glioma-implanted mice, thus suggesting that system Xc-mediated glutamate release in the tumor is involved in seizure production. Mutations or altered activity of SLC17A7 gene can disrupt normal glutamate levels, potentially contributing to excitotoxicity or synaptic dysfunction.

In the reference study, Feyissa et al.[12] investigated the SLC17A7 gene using transcriptome analysis (gene sequencing) of intraoperative human brain tissue from nine patients with glioma-related seizures, comparing the results to tissue from eight glioma patients without seizures. They reported a significant overexpression of SLC17A7 in the seizure group.
In contrast, we aimed to assess the mRNA expression of this gene using RT-PCR instead of gene sequencing; however, we were unable to successfully isolate the mRNA despite multiple attempts.

Possible Reason for Failure:

- Alternative Splicing: The transcript expressed in gliomas may differ from the region targeted by our primers. If the primers are designed to amplify regions subject to alternative splicing, they may fail to bind effectively, resulting in unsuccessful amplification.
- Unstable mRNA: microRNA could regulate the stability of SLC17A7 mRNA, affecting detection if the isoform targeted is unstable.
- Tumor Heterogeneity: The transcriptome analysis by Feyissa et al. may indicate regional overexpression, which might not be uniform across all tumor samples.

This may also suggest that although the SLC17A7 gene shows DNA-level amplification (as reported in the study by Feyissa et al.[12], it may not ultimately result in increased mRNA and hence increased protein expression. Consequently, another gene involved in the glutamate pathway might be responsible for the elevated glutamate levels in the tumor microenvironment11 that contribute to seizure activity.

CXCL8 gene: The CXCL8 gene codes for interleukin-8 (IL-8), a protein that plays a key role in inflammation. IL-8 is secreted by tumor cells, where it checks tumor growth, invasion, and metastasis.

Few studies done in normal neuronal tissue of mice show that CXCL8 might lead to increased neuronal excitability and seizures.[26,27] CXCL8 codes for IL-8 which acts on TRPV1 receptors on neurons causing intracellular sodium elevation, increasing neuronal excitability and seizures. In addition, IL-8 upregulates NMDA glutamate receptor again contributing to increased neuronal excitability.

However, in our study, CXCL8 downregulation was seen more in glioma with seizures (64%) than glioma without seizures (44%) suggesting that CXCL8 downregulation might contribute to seizure development. A possible explanation of why does this gene cause seizure in normal neuronal tissue mice but inhibits seizures in glioma tissue of humans could be one of these hypotheses:

- Promotor or repressor sequence before the gene might be present in glioma tissue and not in normal neuronal tissue.
- Differential RNA splicing
- Differential translation of protein
- Different mechanisms in mice and humans

In the study by Feyissa et al.[12] transcriptome analysis of intraoperative human glioma tissue demonstrated significant downregulation of CXCL8 expression in patients with glioma with seizures (n = 9) compared to those with glioma without seizures (n = 8), a finding that correlates well with our result.

The observation that CXCL8 downregulation occurred in 64% of patients in the glioma with seizures group, compared to 44% in the glioma without seizures group, may suggest a potential contributory role of CXCL8 downregulation in seizure development, although the difference was not statistically significant. Assuming this hypothesis is valid, two key questions arise:

The first question is why downregulation was observed in only 64% of cases. Why wasn't it present in all patients with seizures? What could explain the upregulation seen in the remaining 36% of glioma patients with seizures?

One possible explanation is that a specific threshold of CXCL8 downregulation may be necessary for seizures to manifest. In 34% (n = 9) of patients who experienced seizures despite CXCL8 downregulation, it is possible that the reduction in expression did not reach a critical threshold. As our study involved a comparative qualitative analysis rather than a quantitative assessment, we were unable to determine the precise threshold required for seizure occurrence. Another possibility is that antiseizure drugs in these patients might have affected the gene expression by a negative feedback mechanism, in addition to preventing seizures.

Another question is why downregulation, rather than upregulation, of CXCL8 was observed in 44% of patients in the glioma without seizures group, despite the hypothesis that CXCL8 upregulation may exert a seizure-inhibitory effect. One possible explanation is that, although these patients had not experienced seizures at presentation, CXCL8 downregulation might indicate a predisposition to seizures in the future.

Conclusion

CXCL8 downregulation was observed more frequently in patients with seizures than those without, suggesting a possible link to seizure development, although this difference did not reach statistical significance. Additionally, the SLC17A7 gene mRNA could not be reliably detected using RT-PCR in this study, possibly due to its instability or alternative splicing patterns in glioma tissue. This may also suggest that although, SLC17A7 gene shows DNA-level amplification in other studies[2], it may not ultimately result in increased mRNA and hence increased protein expression. Further larger scale mRNA expression studies are required to validate these findings.

Ethical approval obtained from Maulana Azad medical college ethical committee on 5/8/23 via approval number MAMC/234/23.

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