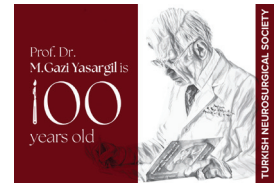




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Investigating the Role of Biomarkers Using Liquid Biopsy in the Diagnosis of Meningiomas

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ABSTRACT

AIM: To evaluate the diagnostic potential of c-MYC, FABP7, GATA4, and MAOB in meningioma patients by analyzing their expression in serum samples.

MATERIAL and METHODS: The study included 20 patients who underwent surgical resection for intracranial meningiomas. Tumor and serum samples were collected during the surgical procedure. Real-time polymerase chain reaction (RT-PCR) was performed to measure the expression of FABP7, GATA4, c-MYC, and MAOB in both tumor tissues and serum samples.

RESULTS: The expression levels of MAOB, c-MYC, and GATA4 were significantly higher in grade 2 meningioma tumor tissues compared to grade 1 tumors ($p=0.031$, $p=0.041$, and $p=0.003$, respectively). Similarly, patients with grade 2 meningiomas had significantly higher MAOB expression in their serum compared to patients with grade 1 meningiomas ($p=0.032$). In addition, the serum levels of FABP7 and MAOB were significantly higher in meningioma patients compared to healthy controls ($p<0.05$).

CONCLUSION: The findings of this study suggest that FABP7 and MAOB expression in serum may serve as diagnostic markers for meningiomas. However, additional studies with larger cohorts are necessary to validate these results.

KEYWORDS: Meningioma, Cancer biomarker, Liquid biopsy, Diagnosis

ABBREVIATIONS: MRI: Magnetic Resonance Imaging, NF2: Neurofibromatosis Type 2, TRAF7: TNF Receptor-Associated Factor 7, SMO: Smoothened, Frizzled Class Receptor, AKT1: AKT Serine/Threonine Kinase 1, KLF4: Krüppel-Like Factor 4, POLR2A: RNA Polymerase II Subunit A, PIK3CA: Phosphatidylinositol-4,5bisphosphate 3-Kinase Catalytic Subunit Alpha, MAOB: Monoamine Oxidase B, FABP7: Fatty Acid Binding Protein 7, GATA4: GATA Binding Protein 4, c-MYC: Cellular-Myc, WHO: World Health Organization, RT-PCR: Reverse Transcription Polymerase Chain Reaction

INTRODUCTION

Meningiomas account for approximately 30% of all primary intracranial tumors and originate from arachnoidal cells of the leptomeninges (33). These tumors

can grow asymptotically for long periods, making early detection a significant challenge (16). Advances in research have shed light on the molecular profile of meningiomas. In addition to the previously established association between meningiomas and mutations in the tumor suppressor gene neurofibro-

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matosis type 2 (NF2), several other genes with recurrent mutations have been identified. These include TNF receptor-associated factor 7 (TRAF7), smoothened receptor (SMO), AKT serine/threonine kinase 1 (AKT1), Krüppel-like factor 4 (KLF4), RNA polymerase II subunit A (POLR2A), and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) (1,3,7,40,44).

Research has also indicated that certain genes, such as monoamine oxidase B (MAOB), fatty acid binding protein 7 (FABP7), GATA binding protein 4 (GATA4), and cellular-Myc (c-MYC), are associated with meningiomas and various other tumor types (9). The current diagnostic approaches for meningiomas primarily rely on histopathological analysis and magnetic resonance imaging (MRI). However, radiology-based methods have limitations, as tumors are typically detected only after reaching a certain size. This delay in detection increases the risk of progression from benign to malignant forms, ultimately worsening patient outcomes. High-grade meningiomas are also associated with higher recurrence rates, further complicating management. Additionally, radiologically mimicking tumors can pose challenges to accurate diagnosis (30).

The difficulty in distinguishing tumor grades is another critical issue, as it directly influences treatment decisions. Aggressive surgical resection is recommended for high-grade meningiomas to reduce recurrence, whereas low-grade meningiomas may not require such extensive intervention. Determining the tumor grade prior to treatment is essential. Histological evaluation from surgical tissue sampling remains the gold standard for grading meningiomas. However, surgical procedures carry risks such as hemiparesis and speech problems, making non-invasive diagnostic methods highly desirable (6).

Liquid biopsy has emerged as a promising non-invasive alternative for identifying tumor markers. This method provides valuable information about the molecular and genetic characteristics of malignancies (2,6). Potential biomarkers for meningioma diagnosis include the transcription of genes such as c-MYC, GATA4, MAOB, and FABP7. While previous studies have explored their expression in tumor tissues, little is known about their expression in serum. The aim of this study was to evaluate the use of liquid biopsy by investigating the serum expression of these genes in patients with meningiomas.

■ MATERIAL and METHODS

Patients

This retrospective study included 20 patients who underwent surgical resection for intracranial meningiomas between May 2017 and March 2021 at our clinic. Approval for the study was obtained from the Ethical Committee (No: 05/110), and the research was conducted in accordance with the principles outlined in the Helsinki Declaration (45). All participants provided informed consent before enrollment. Histopathological evaluation confirmed the diagnosis of meningiomas. Clinical data, including patient age, sex, imaging results, histopathological findings, World Health Organization (WHO) grade, Simpson grade, post-surgical complications, and recurrence status, were collected retrospectively.

Tissue and Serum Sampling

Blood samples were collected prior to surgical intervention, and tumor tissues were obtained during surgery. Serum was separated from blood samples by centrifuging at 2100 rpm for 25 minutes. The isolated serum was stored in Eppendorf tubes at -80 °C until further analysis. Tumor tissues were immediately stored at -80 °C following collection.

RNA Isolation from Tumor and Serum Samples

RNA was extracted from tumor tissues using a total RNA purification kit (EcoTech, Australia), while serum samples were processed with a total RNA purification kit (Jena Bioscience, Germany). Complementary DNA (cDNA) was synthesized using a cDNA synthesis kit (Quantabio qScript cDNA, USA). The concentration of cDNA was measured with a NanoDrop spectrophotometer. Expression levels of FABP7, GATA4, c-MYC, and MAOB were quantified using real-time polymerase chain reaction (RT-PCR) with the SensiFAST SYBR No-ROX Kit (Bioline, USA) on the Rotor-Gene Q system (QIAGEN, USA).

Statistical Analysis

Data analysis was conducted using GraphPad Prism 10.13.0 software. Differences between healthy controls and patient samples were evaluated with the Student's t-test. ANOVA was performed to analyze variance among healthy controls and patients with different tumor grades. Mann-Whitney tests were used to compare gene expression levels in tumor samples. Correlations between gene expression in tumor and serum samples, as well as clinical data, were assessed using Pearson's correlation test. A p-value of less than 0.05 was considered statistically significant.

■ RESULTS

Patient Characteristics

The study included 20 patients who underwent surgical resection for intracranial meningiomas. Histopathological analysis classified 11 patients (55%) as having WHO grade 1 meningiomas and 9 patients (45%) as having WHO grade 2. The median age of the participants was 53 years, ranging from 43 to 75 years. Patient characteristics are summarized in Table I. Figure 1 presents the distribution of data for meningioma patients and healthy controls (n=15).

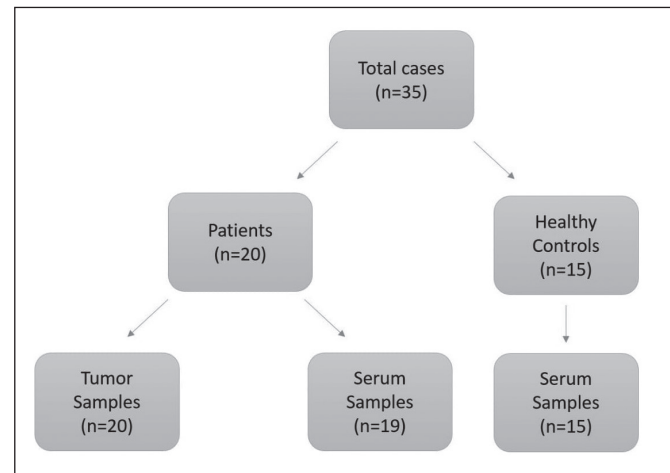
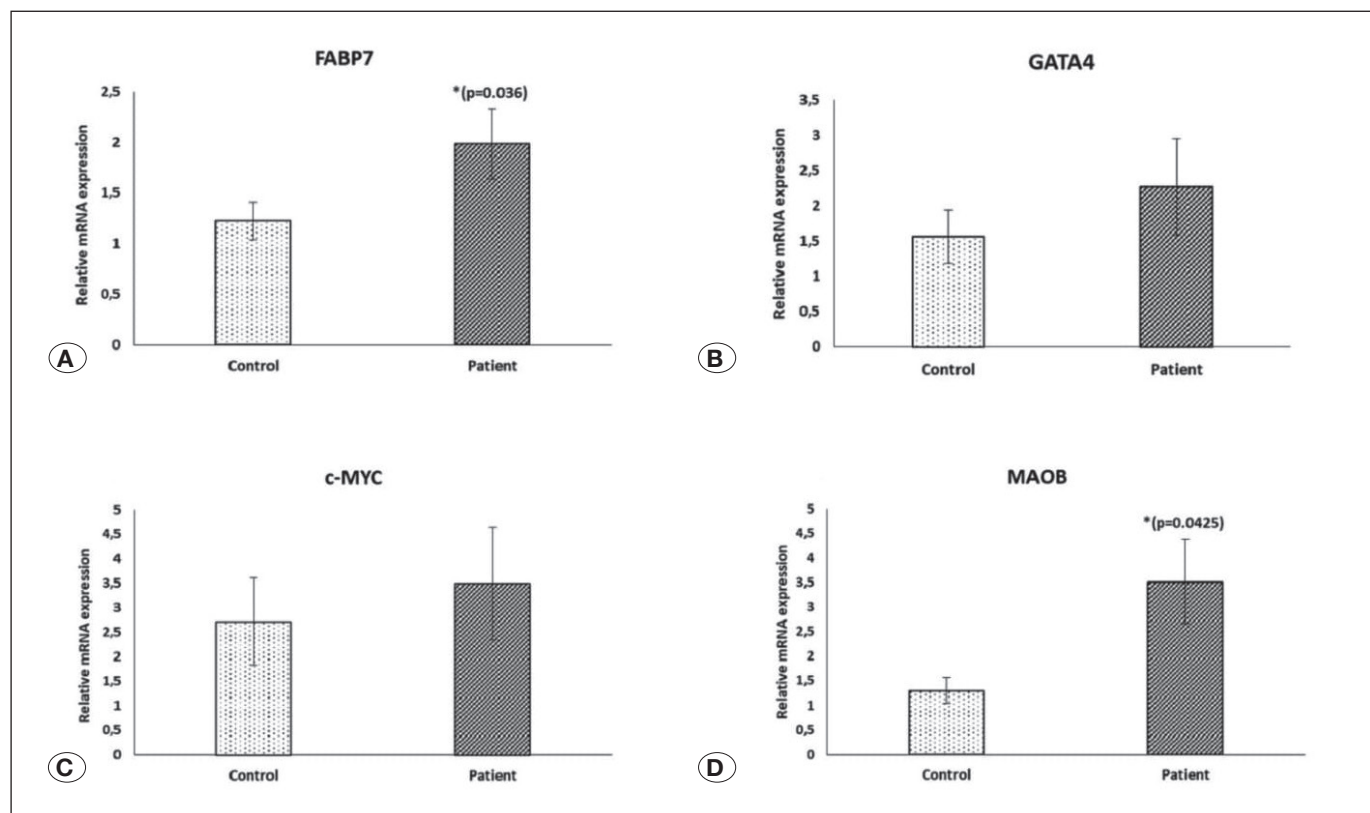
Gene Expression Analysis

To assess whether the expression of FABP7, GATA4, c-MYC, and MAOB is elevated in meningioma patients, serum samples were analyzed. FABP7, GATA4, c-MYC, and MAOB expression levels were higher in the serum of meningioma patients compared to healthy controls. However, only FABP7 and MAOB showed statistically significant differences ($p=0.036$ and $p=0.042$, respectively) (Figure 2).

When expression levels were analyzed by tumor grade, MAOB expression in serum significantly increased with tumor grade ($p=0.032$). Although serum levels of c-MYC, FABP7, and GATA4 also showed an upward trend with tumor grade, these differences were not statistically significant (Figure 3).

Table I: Characteristics of Patients Who Underwent Surgical Resection for Meningiomas

Characteristic	Value
Cases total, n (F/M)	20 (12/8)
Median age (range), years	53 (41-75)
Histological type, Grade	
Atypical /Clear cell, Grade 2, n	9
Transitional, Grade 1, n	8
Angiomatosis, Grade 1, n	1
Fibrous, Grade 1, n	1
Meningothelial, Grade 1, n	1

**Figure 1:** Data stratification.**Figure 2:** mRNA expression levels of **A)** FABP7, **B)** GATA4, **C)** c-MYC, and **D)** MAOB in serum samples of patients with meningioma and healthy controls. FAB7 and MAOB were found to be significantly higher in meningioma patients compared to healthy controls (p=0.036 and p=0.042, respectively).

In tumor tissues, MAOB, c-MYC, and GATA4 expression levels were significantly higher in WHO grade 2 meningiomas compared to WHO grade 1 (p=0.03, p=0.04, and p=0.003, respectively) (Figure 4). No correlation was observed between the gene expression levels and clinical data, such as local tumor control or recurrence rates.

DISCUSSION

The 2021 WHO classification system divides meningiomas into three grades with a total of 15 histopathological subtypes (25). Nine of these subtypes fall under grade 1, while clear cell and chordoid histology are classified as grade 2. Rhabdoid and papillary histologies are no longer used as criteria for

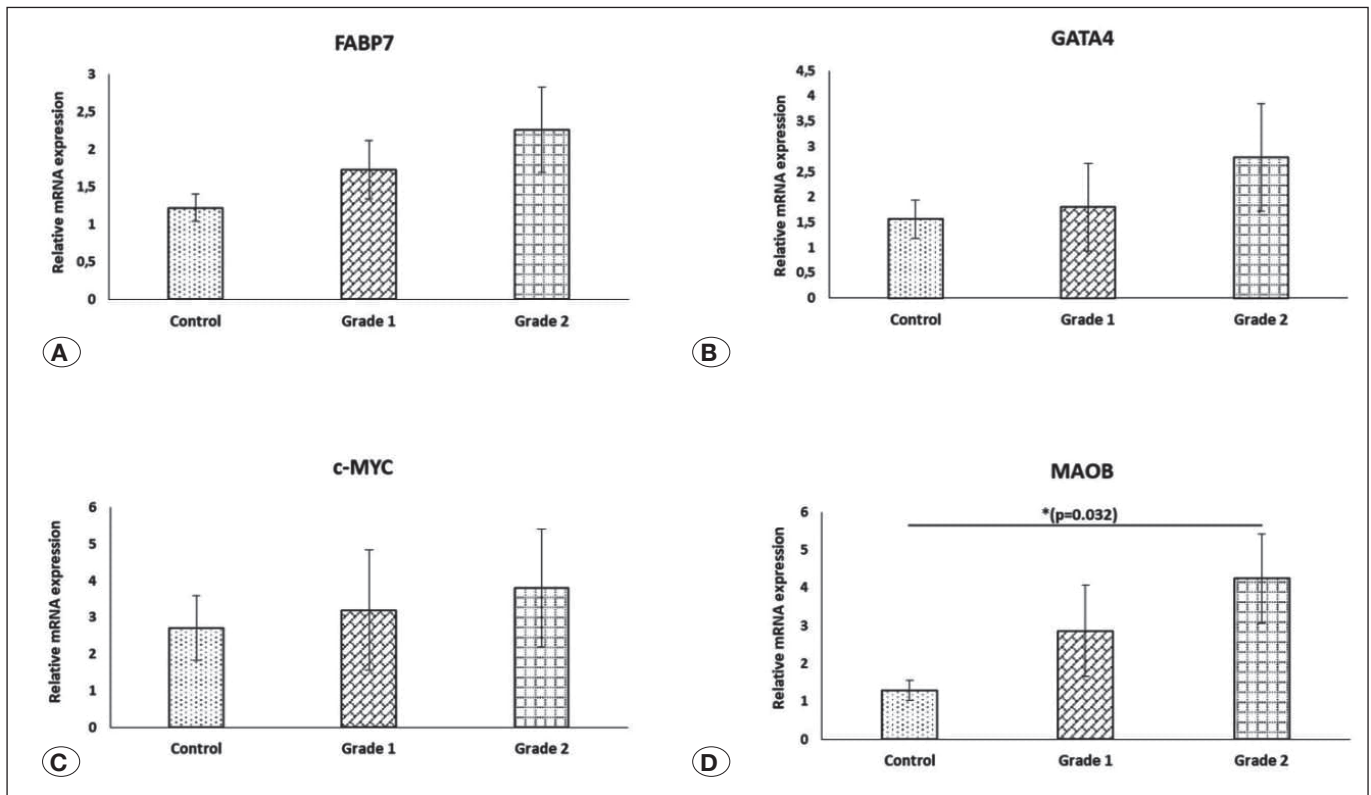


Figure 3: Comparison of mRNA expression levels of **A)** FABP7, **B)** GATA4, **C)** c-MYC, and **D)** MAOB between WHO grade 1 meningioma patients' serum samples and WHO grade 2 samples. Only MAOB gene expression in the serum was significantly increased in correlation with an increase in meningioma grade ($p=0.032$).

grade 3 classification. Most meningiomas are categorized as WHO grade 1, with an 86% five-year progression-free survival (PFS) rate regardless of the extent of resection (EOR) and a 96% PFS following gross total resection (GTR) (15,24,34,36). However, long-term studies indicate that up to 38% of grade 1 meningiomas recur even after gross total resection, highlighting that WHO grade alone may not be sufficient for predicting clinical outcomes (18,20,26,34,36). In contrast, WHO grade 2 (atypical) and grade 3 (anaplastic) meningiomas exhibit more aggressive clinical behavior. These higher-grade tumors are associated with recurrence rates ranging from 20% to 70% within five years, despite surgical resection and adjuvant radiotherapy (5,24). These findings are comprehensively reviewed in a study by Trybula et al. (43).

In this study, we examined whether FABP7, GATA4, c-MYC, and MAOB could be used as diagnostic biomarkers in serum samples from patients with meningiomas through liquid biopsy. We conducted a thorough literature review to identify genes involved in the pathogenesis of meningiomas. Among the many genes studied, we focused on FABP7, GATA4, c-MYC, and MAOB, which have previously been investigated in meningioma tumor tissues and other tumors, particularly gliomas. Moreover, the expression of these genes has been found to differ between malignant and benign forms, suggesting they could serve as potential biomarkers for early detection and diagnosis of meningiomas.

Four genes, c-MYC, FABP7, GATA4, and MAOB, have been implicated in meningioma grades using tumor tissue samples, but their roles in diagnosis, staging, and prognosis of meningiomas are still not fully understood (9,29,31). Additionally, this correlation has not been explored in serum samples. To our knowledge, this is the first study to investigate the diagnostic potential of liquid biopsy for c-MYC, FABP7, GATA4, and MAOB in patients with meningiomas. Our findings showed that FABP7 and MAOB levels were significantly higher in the serum of meningioma patients compared to healthy controls.

The c-MYC protein is a regulator of cellular growth and metabolism. Mutations in c-MYC can lead to cancer development. Overexpression of c-MYC has been observed in glioblastomas, anaplastic meningiomas, atypical meningiomas, and medulloblastomas (19,28,41). This protein promotes cellular changes that can result in neoplasia, contributing to poor clinical outcomes (31). A study by Nagashima et al. examined c-MYC expression in tumor tissues from 20 patients with meningioma, including 17 grade 1, two grade 2, and one grade 3 tumors. Their results showed no c-MYC expression in grade 1 meningiomas, while higher expression levels were associated with tumor recurrence, malignancy, and aggressive progression. However, c-MYC-expressing cells were found to be distinct from proliferating cells, suggesting alternative roles such as involvement in apoptosis rather than direct tumor growth (28). Cai et al. found that in meningiomas, c-MYC

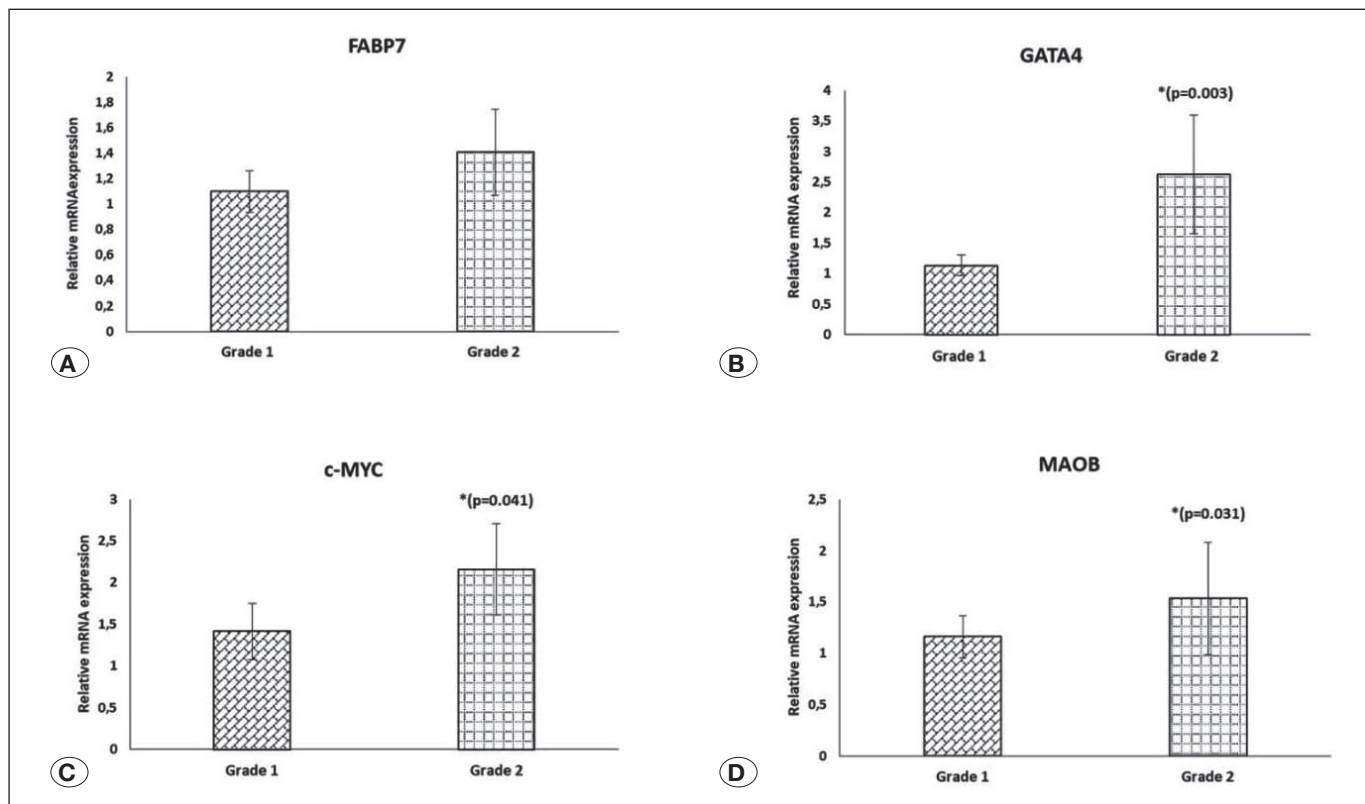


Figure 4: Comparison of mRNA expression levels of **A)** FABP7, **B)** GATA4, **C)** c-MYC, and **D)** MAOB in meningioma tumor samples between WHO grade 1 and WHO grade 2 tumors. The MAOB, c-MYC, and GATA4 genes were significantly higher in WHO grade 2 meningiomas compared to WHO grade 1 ($p=0.03$, $p=0.04$, and $p=0.003$, respectively).

is targeted by RIZ1, which acts as a negative regulator of the ubiquitin-binding enzyme E2C/UbcH1 (4). RIZ1, also known as PRDM2 or KMT8, is a tumor suppressor that functions in transcriptional repression by methylating histone H3 at lysine 9 (47). In our cohort, we found that c-MYC expression was significantly elevated in the tumor tissues of WHO grade 2 meningiomas compared to WHO grade 1 meningiomas ($p=0.04$). However, no statistically significant differences were observed in c-MYC expression between serum samples from meningioma patients and healthy controls. Additionally, while serum c-MYC levels were higher in patients with WHO grade 2 meningiomas than those with grade 1, this difference was not significant.

FABP7 is a small cytoplasmic protein with a molecular weight of 15 kDa and is highly expressed in astrocytes (9). The fatty acid binding protein (FABP) family facilitates the uptake, transport, metabolism, and storage of long-chain fatty acids within cells. In various cancers, FABP7 expression can increase up to 20-fold and is typically associated with a poor prognosis (14). This protein, widely recognized as a marker for neural stem cells, is predominantly found in glioma stem cells cultured using the sphere method (8). In glioblastoma samples, the FABP7 promoter undergoes hypomethylation, leading to overexpression of FABP7 mRNA, which is linked to reduced survival and greater tumor invasiveness (10,21,23). In meningiomas, FABP7 expression is notably higher in grade III

and grade II tumors compared to grade I (9,22). Additionally, it is upregulated in atypical meningiomas compared to benign forms. Markers such as Ki67, PCNA, mitotic index (MI), microvessel density (MVD), BFABP, and COX2 are significantly associated with both FABP7 expression and tumor grade. These correlations between fatty acid transport, eicosanoid metabolism, and proliferation markers like Ki67 and mitotic index suggest that fatty acids play a role in meningioma progression (32). A study by Dunn et al. (9) found FABP7 levels to be eight times higher in grade 3 meningiomas compared to grade 1. Our findings indicated that serum FABP7 levels were notably higher in meningioma patients compared to healthy controls. While serum FABP7 levels were elevated in patients with WHO grade 2 meningiomas compared to those with WHO grade 1, this difference did not reach statistical significance. Furthermore, FABP7 expression in tumor tissue samples did not show any significant difference between WHO grade 2 and WHO grade 1 meningiomas.

Monoamine oxidase (MAO) catalyzes the deamination of compounds in the brain and peripheral tissues, producing hydrogen peroxide (H_2O_2) as a byproduct (39,42). MAO-B activity was found to be significantly higher in glioblastoma tissues compared to postmortem control brains ($p<0.01$) and meningiomas ($p<0.001$). No significant differences were observed in MAO-B activity between glioblastomas ($n=11$), low-grade astrocytomas ($n=3$), and anaplastic astrocytomas ($n=6$) (12).

Studies have shown that, compared to normal brain tissue, MAOB activity is markedly elevated in glioblastomas, low-grade astrocytomas, and anaplastic astrocytomas. However, meningioma tissue does not exhibit increased MAOB activity relative to control brain tissue (27). In their study, Sharpe et al. highlight these findings (38). On the other hand, a study by Dunn et al. reported that grade 3 meningiomas displayed approximately 37 times more MAOB expression than grade 1 meningiomas. Minimal or no MAOB expression was detected in grade 1 meningiomas, whereas grade 3 meningiomas showed a significant increase, consistent with western blotting results (9). Consistent with their findings, our study demonstrated that serum MAOB levels were significantly elevated in meningioma patients compared to healthy controls. Furthermore, serum MAOB expression was notably higher in patients with WHO grade 2 meningiomas compared to those with WHO grade 1 tumors. Additionally, MAOB expression in tumor tissue samples was significantly greater in WHO grade 2 meningiomas compared to WHO grade 1 meningiomas.

The transcription factor GATA4 suppresses the expression of the miR-497-195 cluster in stem cells, which helps maintain cellular function. Studies have shown that GATA4 is overexpressed in malignant meningiomas, where it inhibits miR-497-195 expression and promotes cell viability (13,29), as discussed in the review by Halabi et al. (17). Negroni et al. reported that in patients with high-grade meningiomas, serum extracellular vesicles (EVs) exhibited reduced miR-497 levels due to elevated GATA4 expression in these tumors. GATA4 upregulation in high-grade meningioma samples leads to an increase in cyclin D expression (29). Treatment with NSC140905, a small molecule inhibitor of GATA4, reduced cyclin D1 expression and decreased meningioma cell viability in vitro (46). These findings suggest that GATA4 could serve as a biomarker for meningiomas, especially in more aggressive cases (29).

In our study, GATA4 expression in tumor tissue samples was significantly higher in patients with WHO grade 2 meningiomas compared to those with WHO grade 1 meningiomas. However, we did not observe significant differences in GATA4 expression in serum samples between meningioma patients and healthy controls. Although serum GATA4 levels were elevated in WHO grade 2 patients compared to WHO grade 1, the difference was not statistically significant.

Different WHO grades of meningiomas exhibit distinct protein profiles, which can help identify potential protein-based biomarkers (18), as reviewed by Halabi et al. (17). Liquid biopsy is a non-invasive technique for detecting tumor markers in body fluids like blood and cerebrospinal fluid (CSF) (35). This method can identify circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA). Recent developments have shown its effectiveness in diagnosing cancers such as lung, breast, and colorectal cancers (37). Despite these advancements, the blood-brain barrier complicates the use of liquid biopsy for brain tumors by limiting the detection of tumor markers. Nevertheless, liquid biopsy remains a promising tool for brain tumor diagnosis, early detection, and recurrence monitoring (11).

We also examined potential correlations between gene expression and clinical data. However, no significant associations were found, likely due to the limited number of patients in our cohort. Our study has several limitations. First, the sample size was relatively small. Second, because we included consecutive patients, there were no patients with WHO grade 3 meningiomas, which may have influenced the results. Third, we used RT-PCR as the sole method for gene detection in this preliminary study. Some of our findings also differed from previously published data, which may be attributable to the small cohort size. Moving forward, we plan to expand the study by including more patients and performing additional confirmatory analyses.

CONCLUSION

Our findings indicate that FABP7 and MAOB serum expression levels have the potential to serve as diagnostic biomarkers for meningiomas. Despite these promising results, further research with larger cohorts and additional confirmatory analyses is essential to validate the clinical utility of these biomarkers.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: HK, BK, MAH

Data collection: KA, GG, MAH

Analysis and interpretation of results: SM, IK, HK, BK, EBE, MAH

Draft manuscript preparation: HK, SM, IK, BK, KA, GG, MAH

Critical revision of the article: MAH

Other (study supervision, fundings, materials, etc...): HK, SM, IK, BK, KA, GG, MAH

All authors (HK, SM, IK, BK, KA, GG, EBE, MAH) reviewed the results and approved the final version of the manuscript.

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