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Metabolomics-based liquid biopsy reflects molecular alterations induced by meningioma

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Abstract

Meningiomas (MGMs) account for around 36% of all primary central nervous system tumors. Currently, imaging techniques are the primary method for detecting the presence of MGM, even when it recurs. This study aimed to identify plasma metabolites related to the presence of MGM, searching for a simpler approach to detect molecular alterations in the blood linked to MGM. For that, plasma samples were evaluated through untargeted metabolomics using Mass Spectrometry. Analysis was performed on samples from 51 MGM patients and 50 healthy individuals to identify tumor-related metabolites, which were later identified through tandem mass spectrometry, database verification, and scientific literature. The selected molecules were verified for their potential as MGM biomarkers through Area Under the Curve (AUC) analyses. Three metabolites with the potential to act as MGM biomarkers were identified: hydroxymethyluracil (*m/z* 143; AUC = 0.93), ganglioside (*m/z* 1116; AUC = 0.81), and sulfatide (*m/z* 931; AUC = 0.682). The AUC values for hydroxymethyluracil and ganglioside suggest that these molecules have the potential to differentiate patients with MGM from healthy individuals. These results open a new possibility for identifying tumor biomarkers in the plasma of patients with MGM, especially considering the prospect of patient follow-up.

Keywords Meningioma, Metabolomics, Liquid biopsy, Biomarkers, Plasma

1 Introduction

Meningiomas (MGMs) account for approximately 36% of all cases and 53% of non-malignant central nervous system (CNS) tumors [1] (Maggio et al., 2021). The World Health Organization (WHO) classifies MGMs into grades 1, 2, and 3, based on their malignancy [1, 2]. MGMs are mostly grade 1 benign and slow-growing tumors, making up 80.5% of cases [3, 4]. Grade 2 MGM (atypical) accounts for 17.7% of MGMs and are mainly characterized by brain invasion, in addition to increased mitotic activity and at least three of the following features: small cells with a high nucleus-to-cytoplasm ratio, increased cellularity, prominent nucleoli, necrotic focus, and uninterrupted, patternless growth [4, 5] Lastly, grade 3 or anaplastic MGM is a malignant and aggressive form of the disease, accounting for 1.7% of cases, represented by poor patient prognosis

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and recurrence rates of 50–94% [3–5]. Thus, although MGMs are predominantly benign tumors, high-grade MGMs (grades 2 and 3) are associated with increased mortality rates, with estimated 10-year overall rates of 53% and 0%, respectively [1].

Imaging techniques - magnetic resonance imaging (MRI) and computed tomography (CT) - are the diagnostic tools for MGM detection [6, 7]. Although efficient, imaging techniques may be onerous and may not be able to detect the disease in its early stages, especially during the emergence of relapse-first alterations [8, 9]. Conversely, the metabolomics analytical technique presents intrinsic sensitivity, in which minor changes in biological pathways can be detected [10], even if the alterations are still at the molecular level and are not detectable by current imaging techniques. Owing to its high sensitivity, metabolomics offers early insights into biomarkers involved in the mechanisms underlying various physiological states and abnormal processes (diseases) [10, 11]. To verify the possibility of identifying metabolic alterations related to MGMs in a minimally invasive manner, untargeted metabolomics techniques may be useful for detecting and identifying differential plasma metabolites associated with the presence of the disease.

2 Methods

2.1 Patients and samples

This was a transversal study in which blood samples were collected from 50 healthy donors (control – CT group) and 51 patients with meningioma (MGM group: grade 1, $n = 43$; grade 2, $n = 5$; grade 3, $n = 3$) at the Neurosurgery Division of the Clinics Hospital of Botucatu Medical School, UNESP, São Paulo, Brazil.

The inclusion criteria for MGM group were: I – Presence or suspicion of MGM with formal neurosurgical indication; II – possibility of collecting 4 mL of total blood from patients immediately before the surgical procedure, without harming the patient or any other routine procedures; III – possibility of collecting tumor fragments (3 mm^3) during surgical procedure, without any harming to the histopathological analysis or any other routine procedures; IV – total understanding and agreement to participate in the study, expressed through signing the informed consent forms by the patient or legal responsible.

The exclusion criteria were: I – Patients with any other neoplasia different from the previously established; II – patients with recurrent primary CNS tumors previously treated with radiotherapy and/or chemotherapy; III – patients with small tumors whose tumor fragments were scarce or insufficient for histopathological analysis and/or any other routine procedures; IV – patients or legal guardians who did not fully understand the study guidelines or who did not agree to participate in the study.

2.2 Sample preparation, mass spectrometry and statistical analysis

Blood plasma samples were collected on the first day of hospital admission from all enrolled patients before any other procedure. The blood was collected in EDTA-coated tubes, centrifuged at 3000 rpm for 5 min, and the plasma was collected and stored at -80 °C. Thereafter, plasma samples (20 µL) underwent metabolite extraction and ionization according to the methods of Melo et al. (2017) [12]. Finally, for chemical ionization, formic acid 0.1% was added to the final solution, which was then used for mass spectrometry analysis.

After metabolite extraction and ionization, the samples were directly injected into a mass spectrometer (ESI-LTQ-XL; Thermo Scientific, Bremen, Germany) through Electrospray Ionization and analyzed in positive ion mode under the following parameters: flow rate, 10 µL/min; capillary temperature, 280 °C; spray source voltage, 5 kV; sheath gas, 2 arbitrary units; and mass range, 100–1400 *m/z* (mass/charge). Ten analytical replicates were analyzed for each biological sample, resulting in 500 and 510 spectra for the CT and MGM groups, respectively. The spectra were analyzed using XCalibur software (v. 2.4; Thermo Scientific, San Jose, CA, USA).

To identify biochemical differences between the CT and MGM groups, statistical analysis was performed using the online software MetaboAnalyst 5.0 (Pang et al., 2021) [13] with multivariate partial least squares discriminant analysis (PLS-DA). The variable importance in projection (VIP) scores established by PLS-DA were used to select the most important metabolites for distinguishing healthy individuals from patients. A VIP score ≥ 2.5 was defined as the threshold for the analysis. A group of metabolites was selected using the Fold Change (FC) and Student's *t*-test as univariate parameters using a volcano plot, considering FC ≥ 2.5 and p-value < 0.05 as parameters. Finally, to assess the potential of the metabolites to indicate the presence of the disease, a receiver operating characteristic (ROC) curve was generated for statistically significant molecules (indicated by the volcano plot), and the area under the curve (AUC) was evaluated to assess their accuracy. For the ROC curve, only the metabolites with VIP and FC ≥ 2.5 were selected.

2.3 Molecular identification

The selected molecules with the potential to act as biomarkers for MGM presence were identified by *tandem* mass spectrometry (MS/MS) using Mass Frontier software (v. 6.0; Thermo Scientific, San Jose, CA, USA). Specialized metabolomic databases used include the Human Metabolome Database (https://hmdb.ca/), METLIN (https://metlin.scripps.edu), and LIPID Maps (https://www.lipidmaps.org/). After identification, in silico analyses were performed by consulting scientific literature, and the Kyoto Encyclopedia of Genes and Genomes (KEGG; https://www.kegg.jp/kegg/pathway.html) was used to identify the biochemical pathways possibly involved in the pathophysiology of MGMs.

3 Results

3.1 Patient characteristics

The control group consisted of 50 healthy individuals of both sexes, with a median age of 41.5 years (range, 22–80 years), and without comorbidities. The MGM group comprised 18 males (35.3%) with a median age of 53.5 (range, 39–72 years) and 33 females (64.7%) with a median age of 51.5 years old (range, 27–85 years). Both groups were paired according to sex and age depending on the availability of samples. Among the 51 patients with MGM, 42 (82.4%) had grade 1, six (11.8%) had grade 2, and three (5.8%) had grade 3. The incidence of MGM was 1.8 times higher in female than in male patients.

3.2 Differential metabolites profile

PLS-DA multivariate analysis revealed a clear separation between the MGM and CT groups (Fig. 1), suggesting the existence of differential metabolites capable of distinguishing patients from healthy individuals, in addition to allowing the selection of the

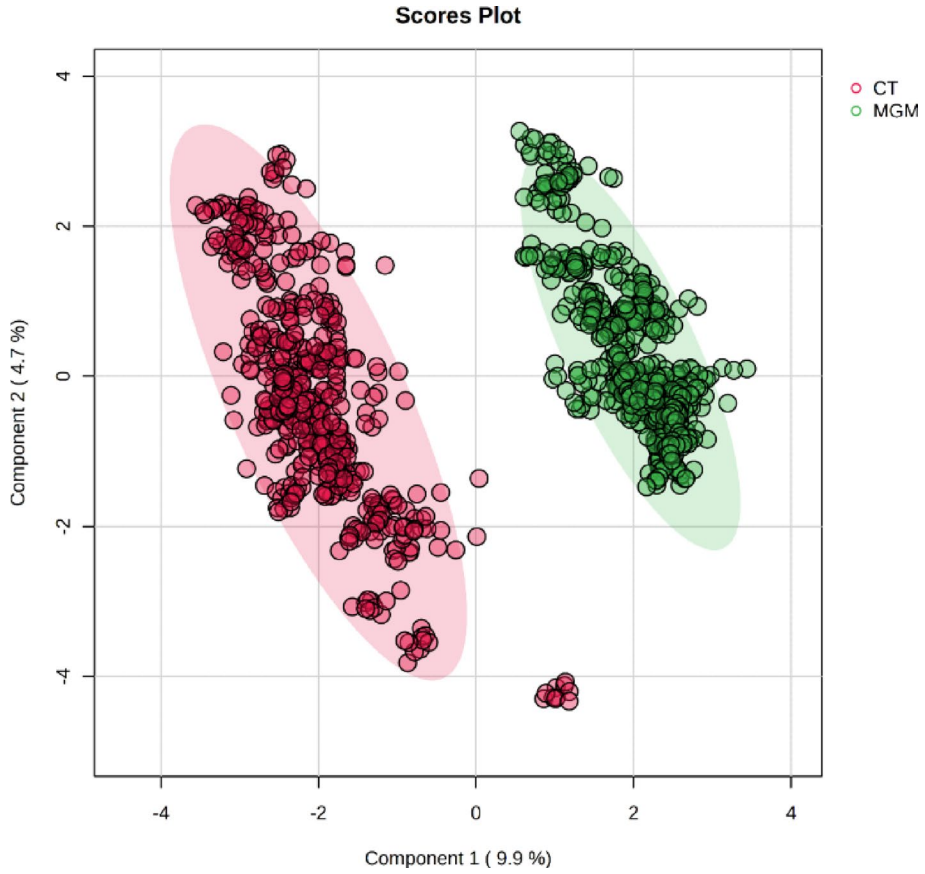


Fig. 1 Clear separation between MGM and CT groups through partial least squares-discriminant analysis (PLS-DA) suggests the existence of differential metabolites capable of distinguishing the groups

most important metabolites according to their VIP scores (Supplementary material Fig. S1).

Intending to better identify and understand the best biomarkers, we generated a volcano plot considering FC > 2.5 and $p < 0.05$ as thresholds (Fig. 2), with the aim of assessing the VIP metabolites with statistical significance.

Then, we selected those with VIP ≥ 2.5 and FC ≥ 2.5 to generate a ROC curve (Fig. 3) to assess the accuracy of this metabolite set in assertively distinguishing patients with MGM from healthy individuals through the analysis of their AUC value.

The *m/z* values used to generate the ROC curve were 172, 102, 143, 931, and 1116; the fragmentation patterns and identities of each biomarker are shown in Table 1 and discussed below. It was not possible to identify *m/z* 172 and 102 because of the absence of corresponding structures in the literature and databases. This represents a challenge and limitation of untargeted metabolomics, as specialized databases do not annotate unknown structures, and many unknown metabolites await discovery [14].

To observe the statistical power of the identified molecules independently, each one of them was tested for accuracy through a ROC curve that provided the AUC value (Fig. 4) and confusion matrix (Supplementary Material). Specificity and sensitivity values were also calculated, altogether with the respective accuracy values (Supplementary Material). Among the three identified metabolites, *m/z* 143 presented the greatest AUC (0.93), followed by ganglioside (AUC = 0.81), and 3-O-sulfogalactosylceramide (AUC = 0.68)

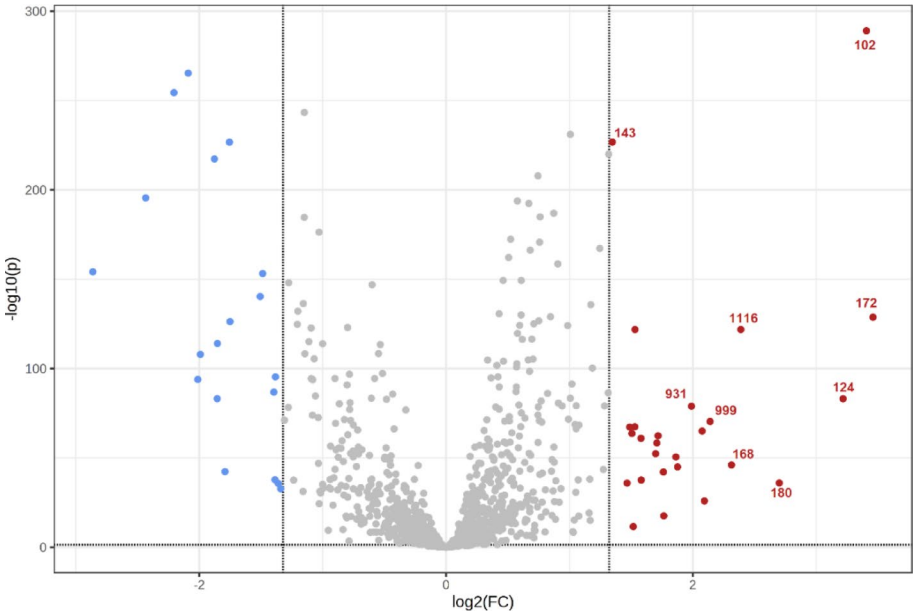


Fig. 2 Volcano plot of the metabolites using a threshold of -2.5 ≥ FC ≥ 2.5 and $p < 0.05$, for the comparison MGM/CT. The red dots correpond to *m/z* values with FC ≥ 2.5, and the blue ones represent metabolites with FC ≤ -2.5. The gray dots represent the *m/z* values that did not attend the p and FC threshold values

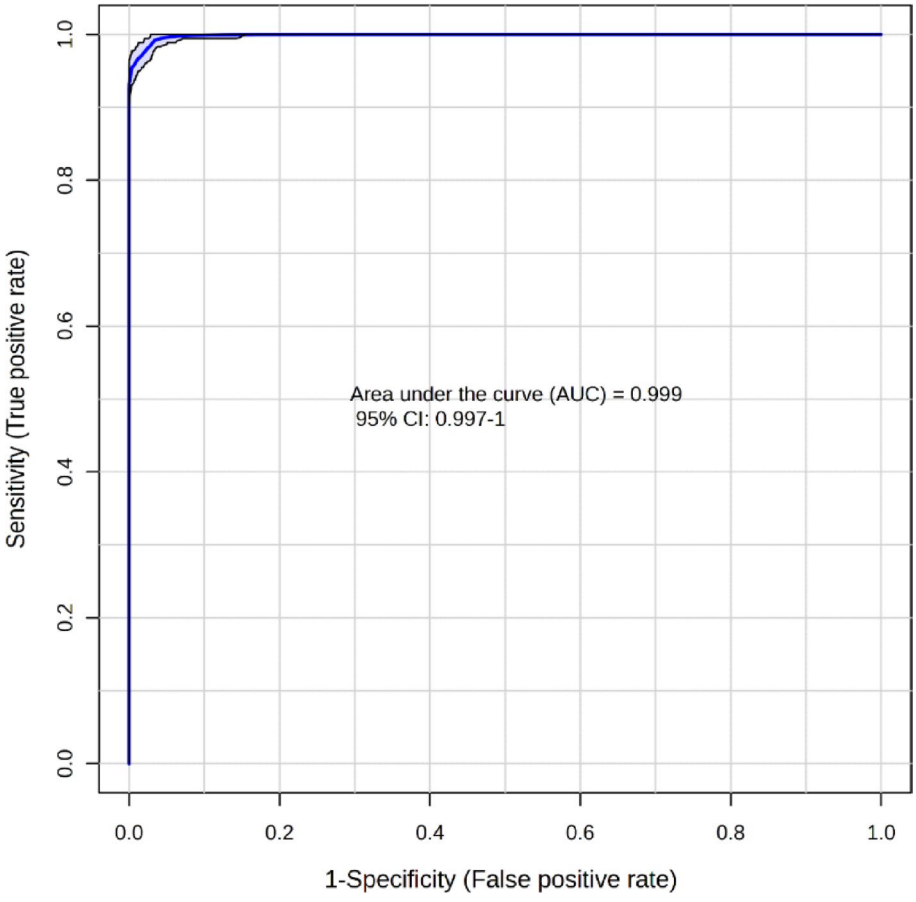


Fig. 3 Receiving operating characteristic (ROC) curve analysis of the selected metabolites (*m/z* 172, 102, 1116, 931, and 143)

Table 1 Proposed plasmatic biomarkers indicative of meningioma presence

m/z	VIP Score	FC	ID	Proposed Metabolite	Formula	Adduct	MS/MS
172	2.5	11.0	–	Unidentified	–	–	–
102	3.5	10.6	–	Unidentified	–	–	–
143	5.5	2.5	MID5456	5-Hydroxymethyluracil	$C_5H_6N_2O_3$	$[M+H]^+$	116-111-117-97-125
931	2.9	4.0	HMDB0000024	3-O-Sulfogalactosylceramide (d42:1)*	$C_{48}H_{93}NO_{11}S$	$[M+K]^+$	310-109-121-720-328-357-410-184
1116	4.1	5.2	MID7148	Ganglioside GA2 (d36:1)*	$C_{56}H_{104}N_2O_{18}$	$[M+Na]^+$	338-804-523-321-112/113

m/z: mass/charge ratio; ID: identifier of the metabolite in the databases researched; MID: METLIN; HMDB: Human Metabolome Database; * (carbon number : double bond number); MS/MS: *tandem* mass spectrometry

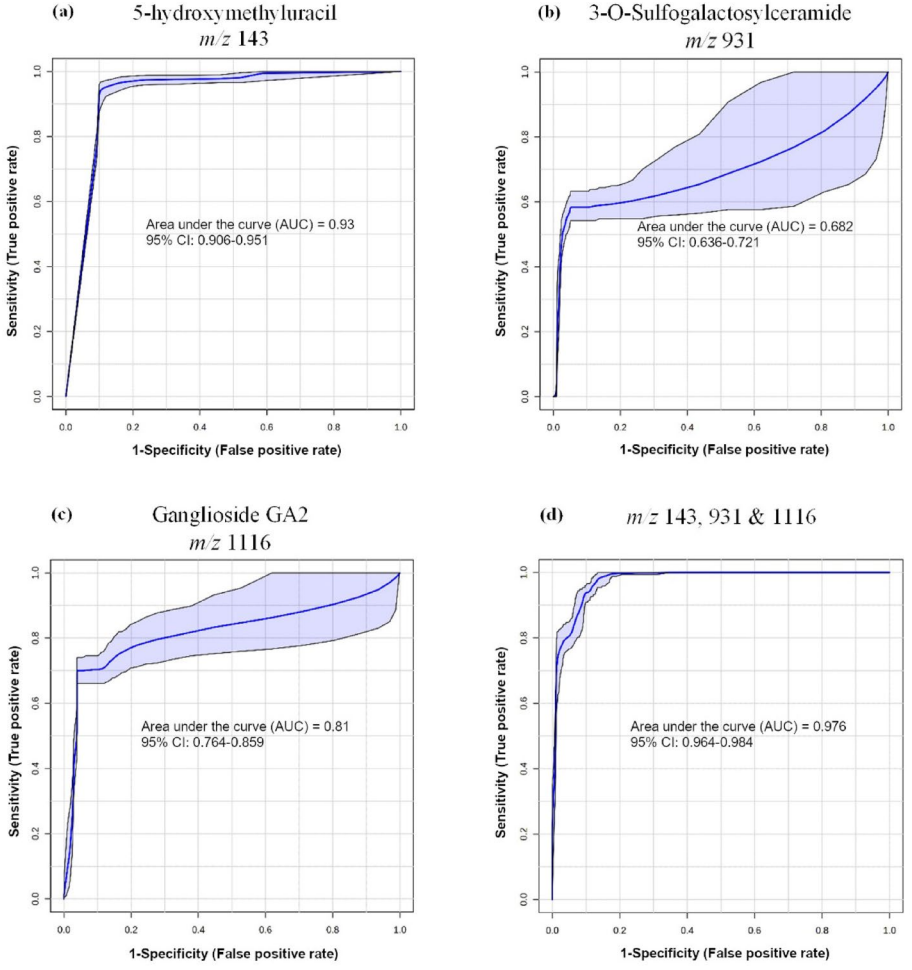


Fig. 4 Accuracy of the identified metabolites through ROC curve analysis **a** *m/z* 143 _ 5-hydroxymethyluracil, **b** *m/z* 931 _ 3-O-Sulfogalactosylceramide, **c** *m/z* 1116 _ Ganglioside GA2, **d** Set of the three identified metabolites evaluated together (*m/z* 143, 931 and 1116)

(Fig. 4). Finally, we generated the ROC curve (Fig. 4d) using only the molecules with *m/z* values of 143, 931, and 1116, aiming to assess the accuracy of this triad in distinguishing patients with MGM from healthy individuals, as well as to ascertain their predictive power when combined (Supplementary Material Fig. S5)

4 Discussion

Among the molecules with the potential to indicate the presence of MGM, we identified 5-hydroxymethyluracil (5-hmU; *m/z* 143), a metabolite produced mainly by interactions with reactive oxygen species (ROS). Its synthesis may occur in two different ways: (i) oxidation/hydroxylation of thymine derived from oxidative stress, resulting in the formation of 5-hmU paired with adenine; or (ii) active DNA-demethylation through the deamination of 5-hydroxymethylcytosine (5-hmC), resulting in 5-hmU mispaired with guanine [15]. Although the DNA repair machinery ensures low concentrations of 5-hmU under physiological conditions, both processes are common in oxidative lesions caused by ROS interactions [16], commonly found in environments of oxidation and methylation imbalance, such as MGM cells [17, 18] and may result in 5-hmU increase.

Loss of 5-hmC may be related to malignant cell transformation in vitro, suggesting that DNA demethylation participates in oncogenic processes [19]. Additionally, increased plasma 5-hmU levels are associated with a greater predisposition to breast cancer [20]. Previous metabolomics data have also revealed increased plasma levels of metabolites in patients with glioblastoma compared to those in healthy individuals [21], suggesting that 5-hmU could act as an epigenetic biomarker [15]. In addition, our data suggest the excellent potential of these metabolites to indicate the presence of MGMs. Altogether, these data highlight the potential of 5-hydroxymethyluracil as a biomarker for the presence of MGM.

Another identified metabolite was sulfatide (*m/z* 931), which originates from ceramide metabolism [22]. Ceramide is an intermediate molecule in sphingolipid metabolism that plays crucial roles in cell signaling, such as inducing apoptosis and cell death, what makes ceramide an important tumor suppressor [23]. Thus, ceramide metabolism can act as an escape route for tumor cells to support tumor proliferation and inhibit apoptosis [24, 25]. Beier and Görögh (2005) [26] suggested a possible escape route used by the tumor cell machinery through the ceramide glycosylation pathway, which involves the conversion of ceramide to galactosylceramide (GalCer) through the activity of the enzyme ceramide galactosyltransferase (UGT8). UGT8 overexpression has been shown to be directly correlated with higher aggressiveness and malignancy in tumor cells [27, 28]. After glycosylation, GalCer is sulfonated into 3-O-Sulfogalactosylceramide [22], a metabolite identified as a potential biomarker for tumor progression in MGMs [29], as well as a biomarker for tumor aggressiveness and invasiveness in glioblastomas [21]. Accordingly, these data support the possibility that 3-O-Sulfogalactosylceramide act as an adjuvant plasma biomarker for different CNS cancers.

Finally, we identified a ganglioside (*m/z* 1116), a subclass of glycosphingolipids located in the outer leaflet of the plasma membrane, which participates in many physiological processes such as cellular adhesion, migration, proliferation, and apoptosis, as well as pathological processes such as cancer [30, 31]. In cancer environments, gangliosides exhibit immunomodulatory potential and are used by tumor cells to escape immune responses and promote tumorigenesis [32]. Considering neural-associated tumors, gangliosides seem to be potentially useful clinical biomarkers for neuroblastomas, for example, neuroendocrine extracranial childhood tumors [33]. However, it is not neural-exclusive, and the metabolite has also been associated with the promotion of tumorigenesis in breast cancer, for example, by acting as a cell surface marker in cancer stem cells [34]. In addition, melanoma cells show increased ganglioside expression, which has

been correlated with enhanced malignant features such as adhesion [35], cell growth, invasiveness [36], and migration [37]. Considering these data along with our results, it is possible to suggest that gangliosides could potentially act as tumor biomarkers, including MGM biomarkers.

Finally, the triad (*m/z* 143, 931 and 1116) accuracy in distinguishing patients with MGM from healthy individuals showed an excellent AUC value (0.97), as shown in Fig. 4d. This result revealed the great potential of the referred metabolites to indicate metabolic alterations in MGMs when evaluated together. Thus, these molecules may be altered simultaneously during the pathophysiology of MGM. Then, these three biomarkers could be considered as a panel of metabolites that might indicate the presence of MGM.

The main limitation of the current study was the small number of patients with grade 2 and 3 MGMs, which should be addressed in future studies. This reflects the characteristic MGM epidemiology, with grades 1, 2, and 3 corresponding to prevalence rates of 80.5%, 17.7%, and 1.7%, respectively [4]. In addition, to increase the confidence of these biomarkers, or even to find more specific biomarkers, it would be necessary to compare them to metabolic profiles from patients with different CNS tumors to understand their role in MGM conditions. Therefore, the next steps include validation of the identified metabolites through targeted metabolomics techniques and verification of whether these serum metabolites might indicate tumor recurrence, with the aim of ensuring a better prognosis for patients.

Metabolomics analyses of plasma samples revealed a set of differential metabolites that could potentially indicate the presence of MGMs with high accuracy. Additionally, our results highlighted the possibility of detecting differential plasma biomarkers under MGM conditions. We suggest that the presence of these molecules in the peripheral blood should be further evaluated over time after resection surgery for patient follow-up to verify their role as indicators of MGM recurrence.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s12672-025-03374-6.

Supplementary Material 1

Author contributions

All authors contributed to the study conception and design. G.A.K., A.N.d.O., F.L.D.-A. and J.D. performed the MS experiments. P.T.H.F., M.A.Z., A.F.G., and A.C.F. performed biofluid collection and selection and provided clinical support. E.O.L., A.C.F., A.F.G., and G.A.K. analyzed the data and prepared figures. G. A. K. and E. O. L. prepared the manuscript. R.R.C. and P.T.H.F. revised the manuscript. R.R.C. provided the infrastructure and methodological support. E.O.L. and A.C.F. designed the study, managed the groups, and supervised the study. All the authors have read and agreed to the published version of the manuscript.

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Data availability

To protect the study participant privacy, the datasets generated during this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the Research Ethics Committee of Botucatu Medical School (CAAE 47991921.0.0000.5411) and was conducted following the recognized ethical principles outlined in the Declaration of Helsinki (1964) and its later amendments.

Consent for publication
All subjects freely provided written informed consent to participate in this study.

Competing interests
The authors declare no competing interests.

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