Original Article

Exploring *IDH1* and *IDH2* Mutations in Paediatric Medulloblastoma

(isocitrate dehydrogenase 1 (*IDH1*) / isocitrate dehydrogenase 2 (*IDH2*) / paediatric / brain tumours / medulloblastoma)

MOTAZ FADUL[1], SALEH BAEESA[2], ALAA ALKHOTANI[3], AMANY A. FATHADDIN[4], AHMED I. LARY[5], BASSAM ADDASS[6], TAGHREED ALSINANI[7], AHMED BAMAGA[8], AHMAD ALBESHRI[5], MOHAMMED M. KARAMI[9], MOHAMMED A. ABUTALIB[10], MAHER KURDI[1]

[1]Department of Pathology, Faculty of Medicine, King Abdulaziz University, Rabigh, Saudi Arabia
[2]Department of Neurosciences, King Faisal Specialist Hospital and Research Center, Prince Saud Al Faisal Street, Jeddah, Saudi Arabia
[3]Department of Pathology, College of Medicine, Umm Al-Qura University, Makkah, Saudi Arabia
[4]Department of Pathology, College of Medicine, King Saud University, Riyadh, Saudi Arabia
[5] Section of Neurosurgery, Department of Surgery, King Abdulaziz Medical City, Makkah Road, Jeddah, Saudi Arabia
[6]Department of Surgery, Faculty of Medicine, King Abdulaziz University, Abdullah Suleiman Street, Jeddah, Saudi Arabia
[7]Department of Neurosurgery, King Fahad General Hospital, Jeddah, Saudi Arabia
[8]Department of Pediatrics, Faculty of Medicine, King Abdulaziz University, Abdullah Suleiman Street, Jeddah, Saudi Arabia
[9]Department of Clinical Physiology, Faculty of Medicine, King Abdulaziz University, Abdullah Suleiman Street, Jeddah, Saudi Arabia
[10]Department of Pathology and Laboratory Medicine, King Abdulaziz Medical City, Makkah Road, Jeddah, Saudi Arabia

Abstract. Medulloblastoma (MB) in children is associated with distinct molecular subgroups, reflecting substantial biological heterogeneity. The presence of isocitrate dehydrogenase 1 (*IDH1*) and *IDH2* mutations in paediatric MB has been rarely reported and not routinely investigated. Our study included 23 samples from paediatric patients diagnosed with MB. Hotspot alterations at codons *IDH1* R132 and *IDH2* R172 were examined using Sanger sequencing following polymerase chain reaction (PCR). The mean age of the patients was 10 years (SD: 4.25), comprising 17 males and 6 females. All cases exhibited classical histological features of MB. β-Catenin expression was observed in four cases (17.4 %), while 19 cases (82.6 %) showed no expression. No statistically significant differences in progression-free survival (PFS) were found between MBs with positive or negative β-catenin expression (P = 0.6). Radiotherapy alone was administered to four patients (17.4 %), while 19 patients (82.6 %) received combined radiotherapy and chemotherapy. The median PFS was 383 days (1 year and 18 days). *IDH1* R132 or *IDH2* R172 hotspot mutations were not detected in any of the samples. The absence of *IDH1* or *IDH2* mutations in paediatric MB may be attributed to differences in mutational profiles and cellular origins in childhood MB, despite its histomolecular similarities with adult MB.

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Corresponding author: Maher Kurdi, Department of Pathology, Faculty of Medicine, King Abdulaziz University, Rabigh, Saudi Arabia. E-mail: Ahkurdi@kau.edu.sa

Abbreviations: 2-HG – D2-hydroxyglutarate (2-HG), α-KG – α-ketoglutarate, CTNNB1 – catenin beta 1, GNAS – guanine nucleotide-binding protein, alpha-stimulating activity (GNAS), IDH – isocitrate dehydrogenase, MRS – magnetic resonance spectroscopy, MYC – myelocytomatosis-protein arginine N-methyltransferase, NADP – nicotinamide adenine dinucleotide phosphate, NGS – next-generation study, PCR – polymerase chain reaction, PTCH1 – protein matched homologue 1, SHH – sonic-hedgehog-activated, SMARCB1 – SWI/SNF-related, matrix-associated, actin-dependent regulator of chromatin, subfamily B, member 1, SMO – smoothened receptor, TCA – tricarboxylic acid, WNT – wingless activated.

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Introduction

Isocitrate dehydrogenase (IDH) enzymes facilitate oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG), playing a crucial role in the tricarboxylic acid (TCA) cycle, glutamine metabolism, lipogenesis, and redox regulation (Koh et al., 2004; Lee et al., 2004; Badur et al., 2018). There are three recognized isoforms of the *IDH* gene. IDH1 is situated in the cytoplasm and peroxisomes, while IDH2 and IDH3 are found in the mitochondrial matrix (Leighton et al., 1969). The active sites of IDH1 and IDH2 have an affinity for isocitrate and nicotinamide adenine dinucleotide phosphate ($NADP^+$), leading to production of α-KG (Hurley et al., 1991). Mutant forms of IDH catalyse conversion of α-KG to oncometabolite D2-hydroxyglutarate (2-HG) instead of α-KG, which hinders α-KG-dependent enzymes, causing changes in histone and DNA methylation (Waitkus et al., 2018). Recognition of substrates depends on the particular amino acid residues found in the active site. In cancer, frequently mutated residues can impact the arginine residue essential for isocitrate recognition, such as R132 for IDH1 and R172 for IDH2 (Hurley et al., 1991; Yan, et al., 2009). Significant progress in cancer genetics has shown frequent mutations in genes encoding IDHs across various human malignancies, such as gliomas, acute myeloid leukaemia (Paschka et al., 2010), cholangiocarcinoma (Borger et al., 2012), chondrosarcoma (Amary et al., 2011) and thyroid carcinoma (Han et al., 2020). The 2021 edition of the World Health Organization (WHO) and European Association of Neuro-oncology (EANO) have categorized diffusely infiltrating gliomas based on *IDH* mutations (Louis et al., 2021). However, *IDH* wild-type tumours are predominant in glioblastomas (Louis et al., 2021). The presence of *IDH* mutations is associated with a more favourable disease prognosis, leading to extended median survival in G4 astrocytomas [*IDH* wild type: 15 months; *IDH* mutant: 31 months] (Han et al., 2020).

The presence of *IDH* in cases of medulloblastoma (MB) has not been definitively established, either due to the rarity of routine investigation of *IDH* in MB patients or the failure of genomic testing panels for tumour sequencing to detect any *IDH* mutation. Numerous genomic studies, encompassing large sample sizes of various brain tumour types, have not identified MB cases with *IDH* mutations (Hayden et al., 2009; Jones et al., 2012). Intriguingly, a recent examination of 490 sequenced MB samples revealed six instances of adult-type MB with $IDH1^{R132}$ mutations (Northcott et al., 2017).

Medulloblastoma is recognized as the most prevalent malignant brain tumour in children, with documented occurrences in adults as well (Kurdi et al., 2023). Extensive genomic studies conducted over the years have led to the identification of four distinct molecular subgroups of MB, namely [Group 1] wingless-activated (WNT-MB); [Group 2] sonic-hedgehog-activated (SHH-MB) with or without *TP53* mutation; [Group 3, GABAergic, increased *MYC* amplification]; and group 4 [Group D, glutamatergic, reduced *MYC* amplification, *CDK6*/*MYCN* amplification], with groups 3 and 4 being more prevalent (Taylor et al., 2012). Through DNA methylation profiling, additional subgroups have been delineated within the four primary molecular groups, each associated with distinct histological and molecular characteristics (Kurdi et al., 2023). Genetic alterations identified in MB include mutations in catenin beta 1 [CTNNB1], protein matched homologue 1 [PTCH1], smoothened receptor [SMO], myelocytomatosis-protein arginine N-methyltransferase [MYC] among others, which play a major role in tumour development and progression (Zhao et al., 2016; Kurdi et al., 2023). Mutations in *IDH1* and *IDH2* are not typically identified as alterations in MB. Specifically, only three reported cases of MB with *IDH1* mutations have been documented in the literature (Snuderl et al., 2015; El-Ayadi et al., 2018; Liserre et al., 2023). These cases involved two adults and one child. All cases were classified as SHH-MB wild-type *TP53* mutation, associated with uncommon mutations such as *SMARCB1* and guanine nucleotide-binding protein, alpha-stimulating activity polypeptide (*GNAS*). Due to the limited instances of *IDH* mutations identified in MB cases among adults and children, our current study aimed to investigate 23 paediatric MB cases for $IDH1^{R132}$ and $IDH2^{R172}$ mutations.

Material and Methods

Selection of patient samples

This research has been approved by a biomedical ethical committee in Jeddah, Saudi Arabia. The study randomly included 23 children (age < 19 years) who underwent radical resection of the tumour and were diagnosed microscopically as medulloblastoma in one medical institution in the period from 2016 to 2022 (Table 1). Patients' clinical data including treatment protocol and progression-free survival (PFS) were obtained from hospital records. All patients had received radiotherapy with or without subsequent chemotherapy. Four patients did not receive radiotherapy as their parents declined the associated chemotherapy regimen. The PFS was assessed from the day of surgical resection to the first day of recurrence if recurrence occurred. Four-µm formalin-fixed and paraffin-embedded (FFPE) tissue sections were cut using a rotatory microtome to be utilized during tissue processing for DNA extraction and Sanger sequencing.

Tissue processing

A. DNA Extraction

DNA was extracted from FFPE samples using the QIAamp DNA Tissue Kit (QIAGEN 56404, Hilden, Germany) following the manufacturer's protocol. DNA concentration and purity were assessed using a NanoDrop spectrophotometer. DNA concentration ranged from

Table 1. Biological data of 23 medulloblastoma patients. PFS: progression free-survival.

Age	Gender	β-Catenin Expression	IDH1/IDH2	Treatment	PFS in Days
11y	Male	Non-Expressed	No Mutation	Radiation + Chemotherapy	200
6y	Male	Non-Expressed	No Mutation	Radiation + Chemotherapy	149
19y	Male	Non-Expressed	No Mutation	Radiation	137
8y	Male	Non-Expressed	No Mutation	Radiation	104
5y	Male	Non-Expressed	No Mutation	Radiation + Chemotherapy	426
4y	Female	Expressed	No Mutation	Radiation	299
9y	Male	Non-Expressed	No Mutation	Radiation + Chemotherapy	284
10y	Male	Non-Expressed	No Mutation	Radiation + Chemotherapy	No Recurrence
3y	Male	Non-Expressed	No Mutation	Radiation + Chemotherapy	432
6y	Female	Non-Expressed	No Mutation	Radiation + Chemotherapy	998
12y	Female	Non-Expressed	No Mutation	Radiation + Chemotherapy	212
8y	Male	Non-Expressed	No Mutation	Radiation + Chemotherapy	956
17y	Male	Non-Expressed	No Mutation	Radiation + Chemotherapy	736
10y	Male	Non-Expressed	No Mutation	Radiation	109
11y	Male	Non-Expressed	No Mutation	Radiation + Chemotherapy	2754
12y	Male	Non-Expressed	No Mutation	Radiation + Chemotherapy	112
15y	Male	Non-Expressed	No Mutation	Radiation + Chemotherapy	No Recurrence
13y	Female	Non-Expressed	No Mutation	Radiation + Chemotherapy	680
17y	Male	Non-Expressed	No Mutation	Radiation + Chemotherapy	971
11y	Female	Expressed	No Mutation	Radiation + Chemotherapy	430
7y	Male	Expressed	No Mutation	Radiation	No Recurrence
7y	Female	Non-Expressed	No Mutation	Radiation + Chemotherapy	No Recurrence
12y	Male	Expressed	No Mutation	Radiation + Chemotherapy	383

12.64 to 287.69 ng/µl, ensuring sufficient material for subsequent applications. The 260/280 absorbance ratios were between 1.71 and 2.14, and the 260/230 ratios ranged between 0.46 and 2.17, indicating variable levels of purity across the MB samples. All centrifugation steps were conducted at 6,000 *g* for 1 minute at room temperature, unless otherwise stated. The samples were placed in 1.5 ml microcentrifuge tubes, deparaffinized with 1 ml of 99 % m-xylene (Sigma-Aldrich 18556, Burlington, MA), vortexed at 17,000 *g* × 2 minutes. The tissue capsule was washed with 95 % ethanol twice before proceeding with the extraction. The deparaffinized tissue was mixed with 180 µl Buffer ATL and 20 µl proteinase K at 56 °C for 60 minutes, followed by 90 °C for 60 minutes. After spinning down, 200 µl of Buffer AL and 200 µl of ethanol (96–100 %) were mixed. The column was washed with 500 µl of Buffer AW1 and 500 µl of Buffer AW2, then centrifuged dry. Finally, 30 µl of Buffer ATE was added to the membrane and centrifuged at 17,000 *g* for 1 minute. DNA was quantified by spectrophotometry, and eluates were stored at −20 °.

B. Sanger sequencing using polymerase chain reaction (PCR)

PCR amplification of *IDH1* and *IDH2* was carried out using primers synthesized by Haven Scientific (Thuwal, Saudi Arabia) (Table 2). The amplification was performed by mixing 2 µl of DNA with 10 µl of EverGreen Universal qPCR Master Mix from Haven Scientific (LOT: 55.0018), 500 nM of each primer, and RNase-free water to a final volume of 20 µl. The PCR procedure was conducted in the QuantStudio™ 5 Real-Time PCR System (A28139, Applied Biosystems, Waltham, MA) under the following conditions: initial denaturation at 95 °C for 3 minutes, followed by 40 cycles of denaturation at 95 °C for 15 seconds, annealing at 56 °C for 60 seconds and extension at 72 °C for 5 minutes. A melt curve analysis was performed to confirm the presence of single PCR products, and selected samples were electrophoresed to validate the presence of single

Table 2. The designed primer sequences used for IDH1 and IDH2 genes

Primer	Primer	Sequence
IDH1	Forward	ACCAAATGGCACCATACGA
	Reverse	GCAAAATCACATTATTGCCAAC
IDH2	Forward	TGTGGAAAAGTCCCAATGGA
	Reverse	AAGAGGATGGCTAGGCGAG

bands. The PCR products were purified using MagPure A4 XP magnetic beads from Magen Biotechnology (Guangzhou, China). In brief, 40 µl of beads were mixed with the PCR product, incubated at room temperature for 5 minutes, subjected to magnetic separation, washed twice with 100 µl of 70 % ethanol, dried, and the DNA was eluted with 20 µl of RNase-free water.

Sanger sequencing was conducted using the Sanger Sequencing Kit (A38073, Applied Biosystems). Purified PCR products (20–80 ng) were mixed with 2 µl BigDye™ Terminator v3.1 Ready Reaction Mix, 1 µl 5X Sequencing Buffer and 2.3 pmol sequencing primer (*IDH1*_FWD or *IDH2*_FWD) in a 15 µl reaction. Sequencing was performed in the VeritiPro™ Thermal Cycler (Applied Biosystems) with the following protocol: 95 °C for 1 minute, 25 cycles of 95 °C for 10 seconds, 50 °C for 5 seconds and 70 °C for 5 minutes. Post-PCR, samples were purified with SAM Solution and BigDye X-Terminator™ Bead Solution, centrifuged, and then processed in a DNA Analyzer (A41046, Applied Biosystems). Sequences were analysed using Sequence Scanner Software 2 (NanoDrop™ in the Microvolume UV-Vis Spectrophotometer, Applied Biosystems). The data were described in values and percentages. The distribution of PFS among MB cases with positive and negative β-catenin expression was also analysed using the Kaplan-Meier curve (KMC). A P value of less than 0.05 was considered statistically significant (IBM SPSS ver. 24 (SPSS Inc., Chicago, IL)).

Results

The mean age of the patients in our study was 10 years (SD: 4.25), comprising 17 males and 6 females. All cases showed classical histological features of MB. β-Catenin was expressed in four cases (17.4 %), and 19 cases showed absent β-catenin expression (82.6 %). Insignificant statistical differences in PFS were observed among all MBs with positive or negative β-catenin expression (P value = 0.6). Isolated radiotherapy was given to four (17.4 %) patients, while combined radiotherapy and chemotherapy were received by 19 patients (82.6 %) (Table 1). The median PFS was 383 days (1 year and 18 days). There was no single *IDH1*^{R132} or *IDH2*^{R172} hotspot mutation identified in any of the 23 MB samples (Suppl. Figs. 1 and 2).

Discussion

Since 2009, researchers have been exploring mutations in *IDH1* and *IDH2* across all central nervous system (CNS) tumours. *IDH* mutations were predominantly observed in high-grade gliomas among CNS tumours (Louis et al., 2021). However, recent studies on MBs have yielded inconclusive results. Yan et al. (2009) and Parsons et al. (2008) investigated 77 cases of MB specifically for *IDH1* and *IDH2* mutations, but no mutations were detected. Hayden et al. (2009) also conducted an analysis combining results from five studies involving more than 2,500 tumour samples from various cancer types, including 1,600 samples of brain tumour. They identified approximately 35 % of CNS tumours with *IDH1* mutations, with the highest frequency in high-grade gliomas. *IDH1* mutations were not detected in any MB case. Additionally, the International Cancer Genome Consortium (ICGC) PedBrain Tumour Project utilized next-generation sequencing (NGS) to examine samples from 125 paediatric MB patients (Jones et al., 2012). None of the screened cases showed *IDH* mutations. However, only three reported cases of MB in the literature showed *IDH* mutations (Snuderl et al., 2015; El-Ayadi et al., 2018; Liserre et al., 2023). The first case involved a 26-year-old adult patient diagnosed with SHH-MB, exhibiting a notably high 2HG concentration on magnetic resonance spectroscopy (MRS) and wild-type *TP53* (Liserre et al., 2023). Analysis of the patient's tumour sample using pyrosequencing revealed an *IDH1*^{R132} mutation, with further screening via NGS identifying a missense mutation in the *GNAS* gene (Liserre et al., 2023). In a study by Sunderl et al. (2015), an adult case of SHH-MB with an *IDH1*^{R132} mutation was reported using NGS. Additionally, another case with an *IDH1*^{R132} mutation was identified through immunohistochemistry. Among 92 MB samples, a single paediatric case of a 13-year-old child diagnosed with SHH-MB wild-type *TP53* was found to have an *IDH1*^{R132} mutation concurrently associated with an *SMARCB1*^{R201G} mutation (El-Ayadi et al., 2018). This case was noted as the sole paediatric MB case with an *IDH* mutation, suggesting the potential presence of such mutations in the paediatric age group. In our current study, Sanger sequencing of 23 paediatric MB cases revealed no mutations in the *IDH1* or *IDH2* genes (Suppl. Figs. 1, 2).

Mutations in the *IDH1* or *IDH2* gene have been linked to the development of the CpG island methylator phenotype (CIMP) in *IDH*-mutant astrocytoma (Turcan et al., 2012). Through their research, Northcott et al. (2017) discovered that *IDH1*-mutant SHH-MBs exhibit a CIMP^{+} status, indicating the epigenetic role these mutations play, similar to findings in other cancer types. Salomao et al. (2018) conducted a study revealing high expression of the *IDH1* gene in group 3 MB samples from patients older than three years of age. The identification of a hotspot *IDH1* mutation in SHH-MB tumours suggests potential differences in mutation rates or underlying genes involved in the development of adult MB compared to those in paediatric cases (Sunderl et al. 2015). The presence of an *IDH* mutation may play a role as an independent factor in the mutagenesis process of MB. The correlation of *IDH* mutations with less aggressive behaviour and favourable outcomes in adult brain tumours could explain the older age at diagnosis and slower tumour growth, which are typically uncommon in MB. Sunderl and colleagues have recommended further research on *IDH1* and *IDH2* mutations in paediatric MB to better understand the pathogenetic mechanisms associated with *IDH* alterations in MB (Sunderl et al. 2015). Despite molecular similarities, MB may exhibit a

distinct mutation spectrum in adults compared to children. Therefore, a meticulous correlation of sequenced samples with clinical data is crucial for identifying driver mutations and potential therapeutic targets.

Complementary diagnostic methods, such as NGS, play a crucial role in capturing broader mutational landscapes in paediatric MB tumours compared to traditional methods such as Sanger sequencing (Haltom et al., 2020). NGS provides high-throughput, comprehensive genomic profiling that can simultaneously detect multiple genetic alterations, including rare mutations, copy-number variations and structural rearrangements. This broad approach enables clinicians to better understand tumour heterogeneity, identify molecular subgroups and tailor personalized therapeutic strategies. NGS can also detect *IDH* mutations and offers advantages over Sanger sequencing, which specifically targets only *IDH* mutations while neglecting other potentially significant mutations present in MB tumours (Haltom et al., 2020). Consequently, using NGS in clinical decision-making can significantly enhance precision medicine by guiding targeted treatments, improving patient outcomes and identifying prognostic biomarkers, thereby overcoming the limited sensitivity and specificity associated with Sanger sequencing.

IDH mutations play a significant role in the pathophysiology and management of high-grade gliomas, often indicating a more favourable prognosis compared to their wild-type counterparts (Han et al., 2020). These mutations lead to the production of oncometabolite D-2-HG, which contributes to tumorigenesis. The presence of *IDH* mutations has prompted the development of targeted therapies, such as vorasidenib, a dual inhibitor of mutant IDH1 and IDH2 enzymes (Mellinghoff et al., 2023). In August 2024, the U.S. Food and Drug Administration approved vorasidenib for the treatment of grade 2 *IDH*-mutant gliomas, marking a significant advancement in personalized treatment strategies for these tumours. Because *IDH* mutations are exceedingly rare in MB, the molecular landscape of these tumours has primarily focused on alterations in pathways such as *WNT, SHH,* and *MYC* rather than *IDH* mutations. Consequently, management strategies rely on a combination of surgery, radiation and chemotherapy tailored to the tumour's molecular subgroup and the patient's risk stratification. Further research aimed at identifying *IDH* mutations in paediatric MB before tailoring treatments with IDH inhibitors is strongly encouraged.

Limitation

We acknowledge certain limitations in our study. The small sample size may limit the generalizability of our findings, as larger cohorts could provide a more comprehensive understanding of *IDH* mutations in paediatric MB. While Sanger sequencing is a robust and accurate method for detecting specific hotspot mutations, it lacks the broader mutational coverage of NGS, which can identify novel or unexpected alterations. However, NGS is more expensive, resource-intensive, and requires high-quality DNA, which can be challenging with formalin-fixed, paraffin-embedded (FFPE) samples. Despite these limitations, Sanger sequencing remains a cost-effective, practical tool for focused mutation analysis.

Conclusion

MB in the paediatric population is not linked to *IDH1* or *IDH2* mutations. While childhood MB may display diverse mutational and histogenomic profiles, it still shares certain histomolecular features with adult MB. Further studies with larger cohorts are needed to assess the presence of *IDH1/2* mutations in paediatric MB. These findings emphasize the need for comprehensive molecular diagnostic strategies specifically tailored to paediatric MB. Continued investigation into genetic pathways and diagnostic methods may improve understanding the molecular profiling of the tumour and prognoses for paediatric MB patients.

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by a combined ethical agreement between King Faisal Specialist Hospital and Research Center and King Abdulaziz University in Jeddah, Saudi Arabia [IRB-2020-6].

Availability of data and material

The datasets generated and/or analysed during the current study are available from the corresponding author [MK] on reasonable request.

Authors' contributions

MF and MK conceptualized the study. MK1 and MF contributed to the methodology. MF, MK1, SB provided the data. MK1, MF, analysed the data. MF, MK1, SB, AK, AF, AL, BA, TA, AB, AA, MK2 and MA curated the data, wrote the original draft and reviewed and edited the manuscript. All authors have read and approved the final version of the manuscript.

Conflict of interests

The authors have no relevant conflict of interests to disclose.

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