2-Hydroxyglutarate as an MR spectroscopic predictor of an IDH mutation in gliomas

2-Hydroxyglutarat als MR-spektroskopisch erfassbarer Prädiktor einer IDH-Mutation bei Gliomen

Authors

Jochen Bauer[1], Heiner N. Raum[1], Harald Kugel[1], Michael Müther[2], Manoj Mannil[1,3], Walter Heindel[1]

Affiliations

1 Clinic for Radiology, University of Münster and University Hospital Münster, Münster, Germany
2 Department of Neurosurgery, University of Münster and University Hospital Münster, Münster, Germany
3 Institute for Diagnostic and Interventional Radiology, Caritas Hospital Bad Mergentheim, Bad Mergentheim, Germany

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Correspondence

Dr. Jochen Bauer
Clinic for Radiology, University of Münster and University Hospital Münster, Albert-Schweitzer-Campus 1, 48149 Münster, Germany
jochen.bauer@uni-muenster.de

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ABSTRACT

Background The mutated enzyme isocitrate dehydrogenase (IDH) 1 and 2 has been detected in various tumor entities such as gliomas and can convert α-ketoglutarate into the oncometabolite 2-hydroxyglutarate (2-HG). This neuro-oncologically significant metabolic product can be detected by MR spectroscopy and is therefore suitable for noninvasive glioma classification and therapy monitoring.

Method This paper provides an up-to-date overview of the methodology and relevance of ^{1}H-MR spectroscopy (MRS) in the oncological primary and follow-up diagnosis of gliomas. The possibilities and limitations of this MR spectroscopic examination are evaluated on the basis of the available literature.

Results and Conclusion By detecting 2-HG, MRS can in principle offer a noninvasive alternative to immunohistological analysis thus avoiding surgical intervention in some cases. However, in addition to an adapted and optimized examination protocol, the individual measurement conditions in the examination region are of decisive importance. Due to the inherently small signal of 2-HG, unfavorable measurement conditions can influence the reliability of detection.

Key Points

- MR spectroscopy enables the non-invasive detection of 2-hydroxyglutarate.
- The measurement of this metabolite allows the detection of an IDH mutation in gliomas.
- The choice of MR examination method is particularly important.
- Detection reliability is influenced by glioma size, necrotic tissue and the existing measurement conditions.

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ZUSAMMENFASSUNG

Hintergrund Das mutierte Enzym Isocitrat-Dehydrogenase (IDH) 1 und 2 wurde in verschiedenen Tumorentitäten wie z. B. Gliomen nachgewiesen und kann α-Ketoglurat in den Onkometaboliten 2-Hydroxyglutarat (2-HG) konvertieren. Dieses neuroonkologisch bedeutsame Stoffwechselprodukt ist MR-spektroskopisch nachweisbar und eignet sich deshalb zur nichtinvasiven Gliomklassifizierung und Therapieüberwachung.

Methode Die vorliegende Arbeit gibt einen aktuellen Überblick über die Methodik und Relevanz der ^{1}H-MR-Spektroskopie (MRS) in der onkologischen Primär- und Verlaufsdiagnostik von Gliomen. Anhand der verfügbaren Literatur werden

die Möglichkeiten und Grenzen dieser MR-spektroskopischen Untersuchung beleuchtet.

Ergebnisse und Schlussfolgerung Die MRS kann durch den Nachweis von 2-HG prinzipiell eine nicht-invasive Alternative zur immunhistologischen Analyse bieten und so in einigen Fällen einen operativen Eingriff vermeiden. Neben einem angepassten und optimierten Untersuchungsprotokoll sind aber die individuellen in der Untersuchungsregion vorliegenden Messbedingungen von entscheidender Bedeutung. Aufgrund des inhärent kleinen Signals von 2-HG können ungünstige Messbedingungen die Nachweissicherheit beeinflussen.

Kernaussagen

- MR-Spektroskopie ermöglicht die nicht-invasive Detektion von 2-Hydroxyglutarat.
- Hiermit ist der Nachweis einer IDH-Mutation in Gliomen möglich.
- Besondere Bedeutung kommt der Wahl der MRS-Untersuchungsmethodik zu.
- Die Detektionssicherheit wird beeinflusst von Gliomgröße, nekrotischem Gewebe und den vorliegenden Messbedingungen.

Introduction

Diffuse gliomas are a heterogeneous group of infiltrative brain tumors with high disease- and treatment-associated morbidity and mortality. Low malignant forms often have mutations in the genes that code for the metabolic enzyme isocitrate-dehydrogenase (IDH) [1]. IDH occurs in multiple isoforms and is an important part of the citrate cycle as a result of the catalysis of the conversion of isocitrate to α-ketoglutarate. Tumor-associated *gain-of-function* mutations give the enzyme the ability to catalyze the conversion of α-ketoglutarate to 2-hydroxyglutarate (2-HG) [2, 3]. 2-HG accumulates in tumor tissue and inhibits enzymes that control a broad spectrum of cell functions [4]. Compared to gliomas without IDH mutations, IDH-mutated gliomas have a different molecular pathogenesis with a more favorable prognosis [5, 6, 7, 8]. In gliomas, isoform 1 (IDH1) has only been detected to date in cytoplasm and IDH2 in the mitochondria [9].

The analysis and inclusion of such genetic and molecular markers like IDH status is currently the standard in neuro-oncological tumor boards, particularly at leading oncology centers. This review describes the significance of the metabolite 2-hydroxyglutarate (2-HG), which can be visualized on MR spectroscopy and indicates the presence of an IDH mutation during the neuro-oncological diagnostic workup in addition to molecular pathology in gliomas, even if reliable detection and quantification represent a methodological challenge. For this purpose, representative studies were selected based on a search of the literature in the MEDLINE, EMBASE, SCOPUS, and WEB of SCIENCE databases using the following key words and search operators: Glioma AND (2-hydroxyglutarate OR 2-HG OR 2HG) AND (MRS OR MR spectroscopy). Our own studies and measurements were also included, and the results are summarized in this narrative overview.

Proton MR spectroscopy (^{1}H-MRS) and spectral characteristics of 2-hydroxyglutarate

Proton magnet resonance spectroscopy (^{1}H-MRS or MRS) is a non-invasive method that allows quantification of the concentration of known metabolites, such as metabolites containing trimethylamine – usually collectively referred to as choline (Cho or total Cho/tCho) –, N-acetyl aspartate (NAA or total NAA/tNAA, usually also including N-acetyl-aspartate-glutamate), lactate, and myo-inositol, and thus allows conclusions about proliferation, neural integrity, and energy metabolism (aerobic/anaerobic) of intracranial tissues. This information supplements classic imaging in the case of unclear brain lesions and can be valuable.

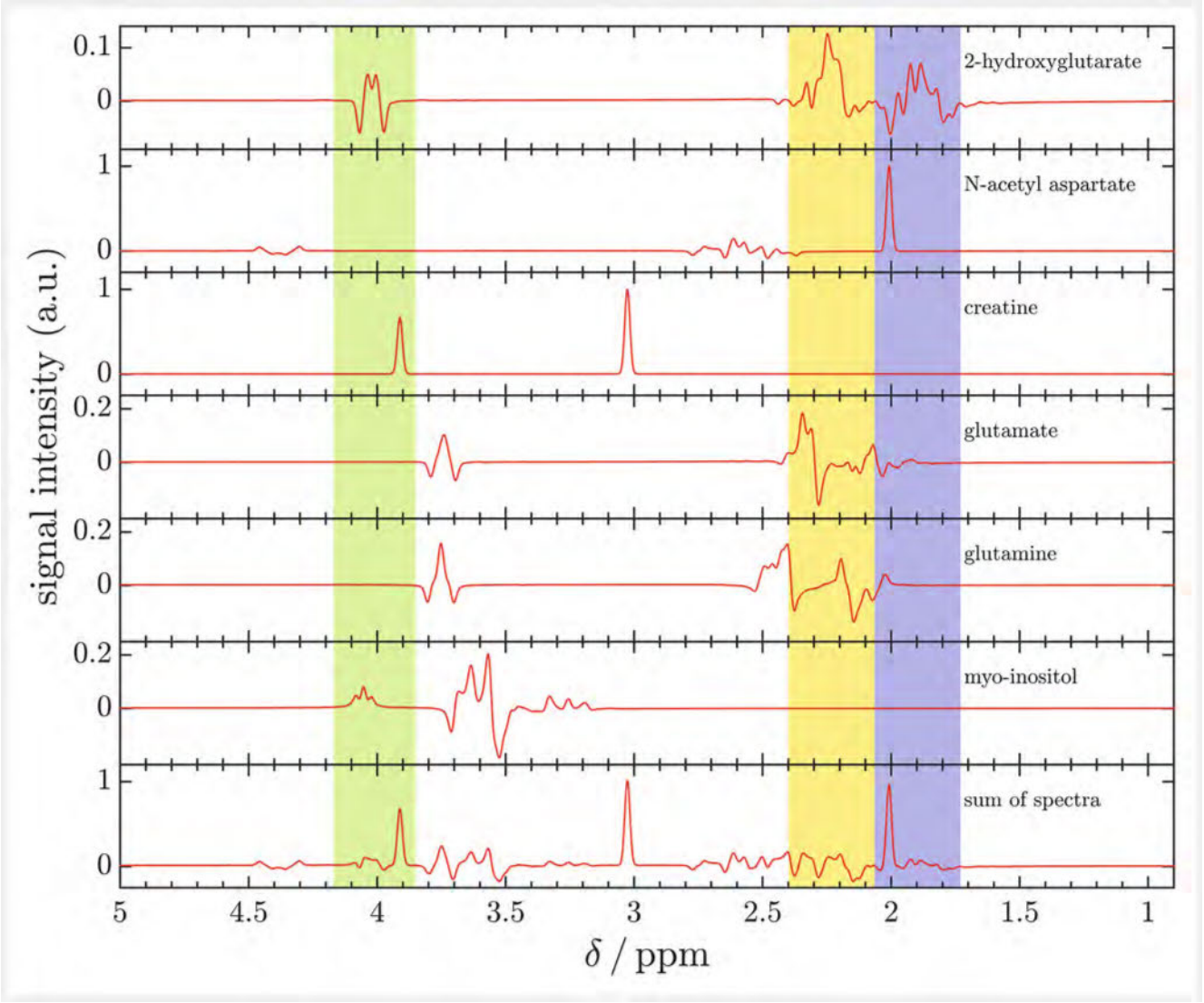
2-hydroxyglutarate or 2-hydroxyglutaric acid has a scalar-coupled spin system with 5 non-exchangeable hydrogen protons. This results in a complex resonance pattern consisting of three multiplets with chemical shifts of approx. 4.02 ppm, 2.25 ppm, and 1.9 ppm in the NMR spectrum [10]. Only a peak of low height is seen in the spectrum due to the splitting (multiplicity) and development of coupling. In addition, in the in-vivo spectrum the 2-HG signals are overlapped or masked by signals of metabolites with a similar chemical shift like NAA (singlet at 2.01 ppm), glutamine and glutamate (multiplets between 2.0 ppm and 2.4 ppm), creatine (singlet at 3.9 ppm), and myo-inositol (triplet at 4.1 ppm) [11]. In ▶ **Fig. 1** the mentioned metabolites are simulated, showing the difficulty of robust, isolated 2-HG detection.

In principle, all three resonances of 2-HG can be used for detection. Due to the spectral proximity to water (4.7 ppm), which occurs in the human brain at a concentration that is approximately 10,000 times higher and therefore must be suppressed by the measurement technology and by postprocessing measures, the 2-HG resonance at 4.02 ppm is only suitable to a limited extent. The typically very prominent NAA resonance also masks the multiplet at 1.9 ppm. The multiplet at 2.25 ppm provides the largest signal so that it is usually used for quantification.

Depending on the MRS acquisition method, 2-HG concentrations of up to 14 mM have been reported [12]. It was determined that gliomas with an IDH2 mutation accumulate more 2-HG than those with an IDH1 mutation [13, 14].

MR spectroscopic detection of 2-HG

In addition to single voxel spectroscopy (SVS), which allows insight into the metabolism in a small cuboidal volume, multi-voxel techniques like spectroscopic imaging (*chemical shift imaging*, CSI, or *MR spectroscopic imaging*, MRSI) are also possible. Typical voxel volumes in SVS are approx. 1–8 cm^3 and can be measured in approximately 3–5 minutes depending on the required signal-to-noise ratio (SNR). In contrast, a total matrix (2 D or 3 D) of voxels, for example, 1 cm^3 in size, with a large total volume of up to 300 cm^3 in the brain being selected and excited, is acquired in spectroscopic

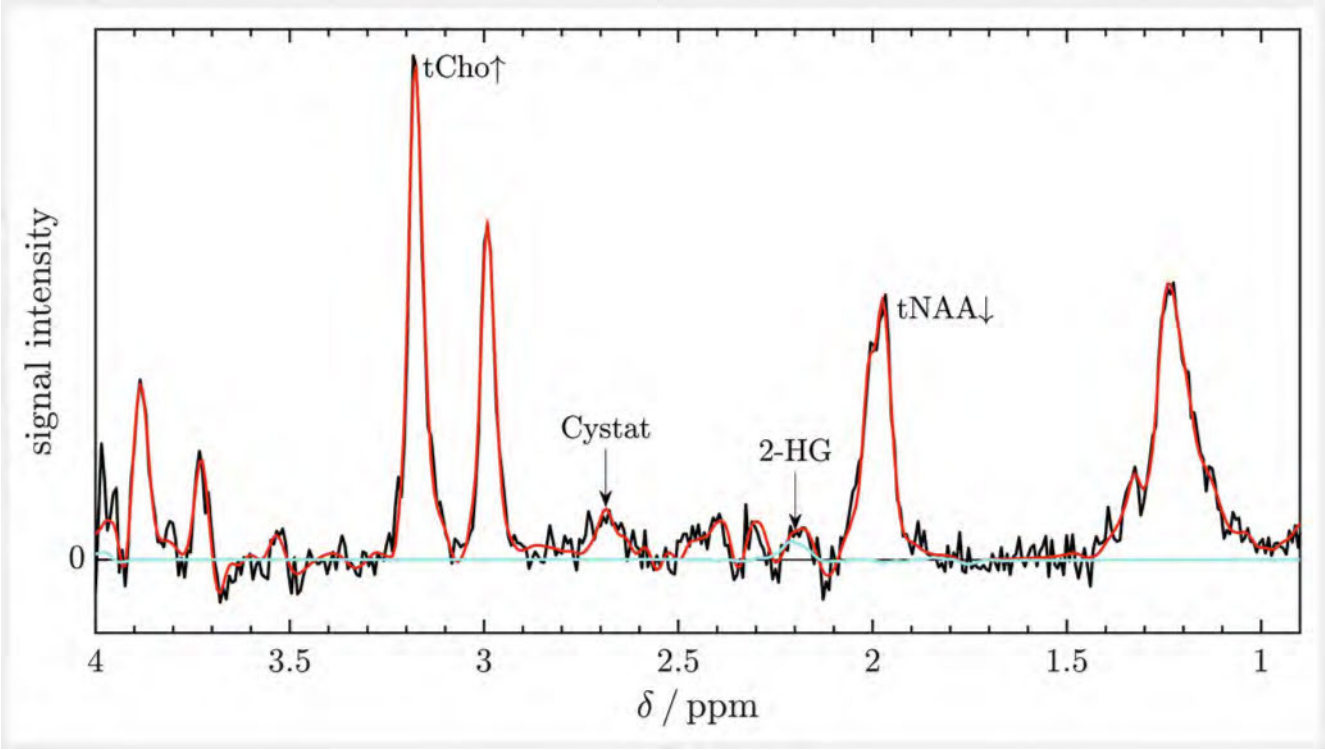


▶ **Fig. 1** Simulation of 2-HG and overlapping resonances of some metabolites. A PRESS sequence with TE1 = 32 ms, TE2 = 65 ms was simulated [10]. The overlapping frequencies are marked in color resulting in overlapping with the displayed, partially more prominent, metabolites in the in-vivo spectrum. The significantly greater line widths (full width at half maximum, FWHM) of the resonance peaks occurring in practice due to the typically imperfect shimming of the measurement volume are not taken into consideration in the simulation. The different scaling of the individual spectra should be taken into account. The real intensity relationships are shown in the sum spectrum (below). Due to the in-vivo concentrations, the overlapping metabolite peaks are typically higher than the 2-HG signal intensity.

imaging. The necessary phase-encoding steps require a significantly longer measurement time. Moreover, the B_0-field can have worse shimming in the case of such a large total volume, which primarily impedes water suppression. The additional spatial information acquired with spectroscopic imaging can be viewed as metabolite maps, usually as metabolite ratios, and superimposed on an anatomical image. For the determination of the absolute concentration of detectable metabolites, SVS is more suitable due to the typically higher spectral resolution provided by the technique and the easier recording of reference signals. Proposed, technically complex MRSI methods like the use of specific readout techniques with acquisition times of almost 16 minutes [15] are suitable only on a limited basis for use in the clinical routine.

An acquisition method used in the clinical routine is the *Point REsolved Spectroscopy Sequence* (PRESS) [16, 17]. Due to the possibility of achieving very short echo times, the *STimulated Echo Acquisition Method* (STEAM) [18] is often also used. However, its signal intensity is only half as high as in PRESS. The *chemical shift displacement* (CSD) issue that occurs when localizing measurement volumes can be reduced by using adiabatic refocusing pulses as in the *semi-Localized by Adiabatic SElective Refocusing* sequence (sLASER or semi-LASER) [19].

The selection of the echo time TE has special significance in all acquisition methods. The literature on 2-HG includes examinations with both a short [20, 21, 22] and long TE [23]. An optimized PRESS version was proposed by Choi *et al.* [10]. With a numeric simulation and subsequent phantom measurements, the times be-



▶ **Fig. 2** In-vivo spectrum of an oligodendroglioma after radiation therapy and chemotherapy acquired at 3 Tesla with PRESS, TE = 97 ms (TE1 = 32 ms, TE2 = 65 ms). In addition to 2-HG detection, the typical tNAA decrease and tCho increase are seen. The main signal at approximately 1.2 ppm is a lipid signal. The fitted basic data signal of 2-HG is shown in cyan. The published resonance of cystathionine (Cystat) indicates a 1p/19q codeletion [24].

tween high-frequency pulses were optimized. Using a total TE of 97 ms, comprised of 32 ms (TE1, between the first and second RF pulse) and 65 ms (TE2, between the second and third pulse), a high rate of detectability could be achieved. ▶ **Fig. 2** shows a spectrum acquired with a PRESS modified according to these requirements.

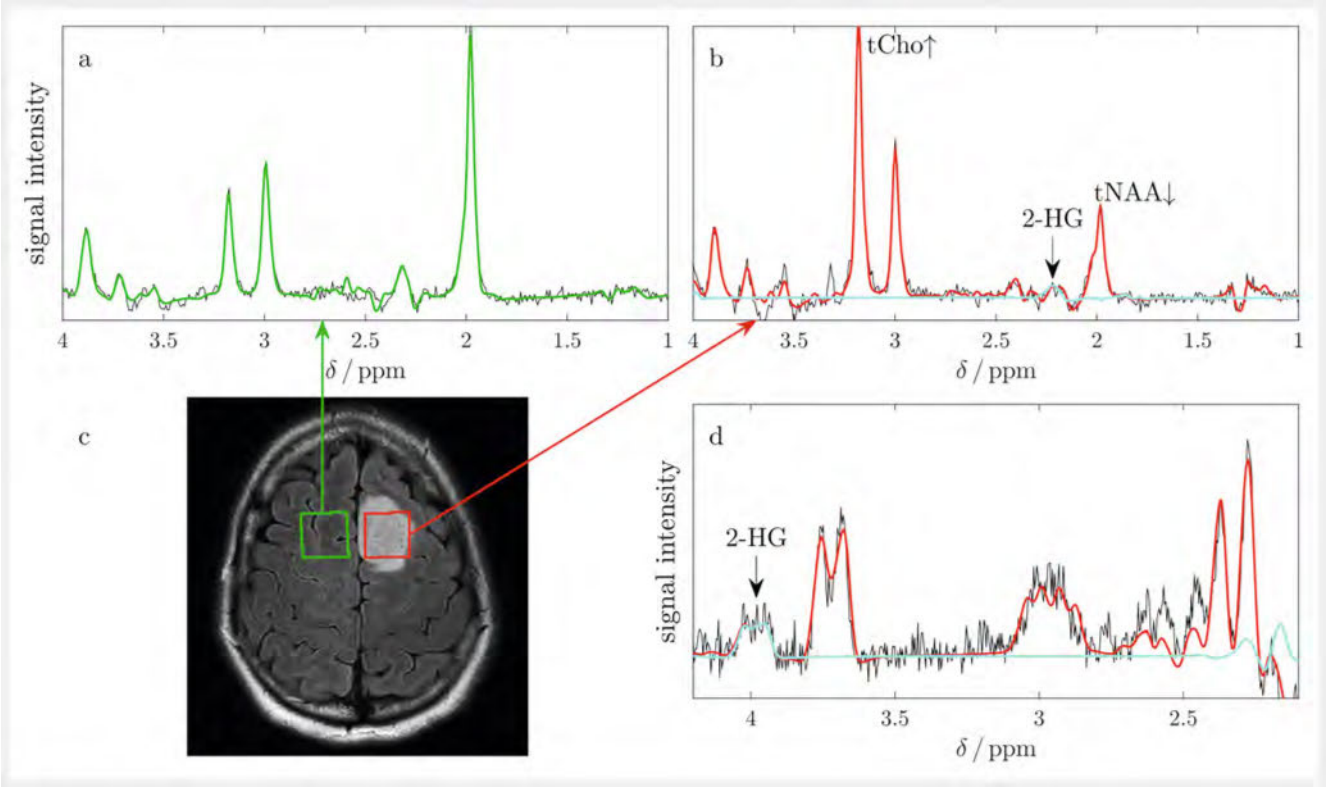
In total, the use of longer echo times seems to result in more reliable results. Suh *et al.* [12] showed a higher false-positive rate and thus worse diagnostic performance for examinations with a short TE. One reason for this could be that, in the case of long echo times, overlapping metabolites like glutamate and glutamine can be better differentiated from the 2-HG resonance pattern at 2.25 ppm as a result of the difference in the development of their scalar coupling pattern (J-coupling).

The Mescher-Garwood method (MEGA) [25] addresses the problem regarding overlapping metabolite signals with a similar chemical shift and is used as MEGA-PRESS and also MEGA-sLASER. In the case of 2-HG, a frequency-selective saturation pulse (ON) is applied to the functional group at 1.9 ppm. As a result, the scalar coupling to the functional group at 4.02 ppm can be refocused (known as editing). In a second experiment, a similar frequency-selective pulse (OFF) in a non-relevant frequency range is emitted. The signal at 4.02 ppm remains unchanged. In the ideal case, subtraction is used to obtain a difference spectrum without unedited or non-scalar-coupled resonance groups (ideally eliminated by subtraction). However, this method is significantly more susceptible to changing and inhomogeneous measurement conditions, e. g., B_0-inhomogeneities or frequency drifts, which occur under clinical examination conditions. In addition, a longer acquisition time and a greater measurement volume are required due to the lower sensitivity. A 2-HG examination with sLASER compared to MEGA-sLASER on a 7-Tesla system showed that the classic, unedited acquisition technique is the more robust method and is thus more suitable for clinical use [26]. However, at 3 Tesla, Branzoli *et al.* [27] were able to show better detection using MEGA-PRESS compared to PRESS.

▶ **Fig. 3** shows the detection of a low-grade astrocytoma with the PRESS and the MEGA-PRESS methods. The optimized PRESS spectrum provides additional information about relevant metabolites like choline, creatine, and NAA, which are eliminated in the MEGA-PRESS difference spectrum. However, it is possible to analyze the OFF spectrum in this regard without the uncoupling pulse.

Quantification

For qualitative assessment of 2-HG, it is often sufficient to detect typical peaks. Additional steps are needed to quantify the 2-HG concentration. A reference with a known concentration in the spectrum is typically needed for this. Creatine or water can be used as the reference signal. Based on the ratio to creatine, which is considered to be constant, acquisition and equipment variables, e. g., enhancement factors, can be cancelled out, and additional



▶ **Fig. 3** MR spectroscopy (3 Tesla) of a low-grade, treatment-naive glioma (red) and the contralateral side (green). An astrocytoma (IDH-mutated, grade 2) was confirmed by immunohistochemistry. **a** Contralateral PRESS spectrum (TE1 = 32 ms, TE2 = 65 ms, (2 × 2 × 2) cm³) and **b** glioma spectrum with elevated tCho, 2-HG, and reduced tNAA. The PRESS spectra were scaled on the basis of the creatine peak at approx. 3 ppm. **c** Anatomical position of the VOI on transverse FLAIR image (field of view 154 mm x 163 mm). **d** Corresponding glioma MEGA-PRESS spectrum ((3 × 3 × 3) cm³, TE = 68 ms, MEGA pulse with 85 Hz bandwidth, ON = 1.89 ppm, OFF = 7.46 ppm). The fitted 2-HG basic data is shown in cyan.

measurements are not necessary. However, the absolute concentration can be estimated only on a limited basis since the creatine concentration between white and gray matter differs greatly [28] and can vary greatly in gliomas and other lesions [29].

In contrast, when using tissue water as an internal reference [30], an additional comparison spectrum without water suppression must be acquired. The water concentration in the voxel can be determined by segmenting anatomical images in gray and white matter and cerebrospinal fluid (CSF) and by including tissue-specific parameters [31]. In the case of masses or lesions, the accuracy of this method is limited when the tissue water content is uncertain. In this case, the water concentration can also be estimated based on a proton density-weighted image in that the average signal intensity of the voxels in the tissue is compared to that of the CSF, whose water concentration on MRI (97 %) is known [32]. The influence of different relaxation effects can result in uncertainty especially in the case of intermediate or long echo times when the tissue-specific transverse relaxation times are not known. This problem can be addressed with an additional T2 measurement and subsequent relaxation correction. Moreover, the metabolite concentration determined via water referencing can be dependent on the pulse sequence used by the manufacturer [33]. This was not observed when determining the ratio to creatine [34].

The processing and quantification of the measured spectra are typically performed with the help of software-based methods in the time or frequency range and can include, in addition to Fourier transformation, signal processing steps like eddy current correction, numeric residual water suppression, frequency and phase correction, apodization, zero filling, and baseline correction [35]. A basic dataset simulated according to the acquisition parameters or measured in vitro and containing all relevant metabolites is adapted to the in-vivo spectrum. The relative *Cramér-Rao-Lower-Bounds* (CRLB) were established to measure the quality of fit.

Reliable detection of 2-HG is sufficient to prove an IDH mutation as additional diagnostic information. Quantification for longitudinal observation of 2-HG concentration during treatment monitoring is significantly more challenging. Data quality that is as constant as possible is required for detection of even slight changes in concentration. Choi *et al.* [36] were able to show a rapid decrease in 2-HG concentration in oligodendrogliomas as a reaction to chemotherapy, while this decrease was slower in astrocytomas. The use of IDH inhibitors for tumor treatment was able to be successfully tracked by Di Stefano *et al.* [37] based on 2-HG concentration dynamics.

Detection reliability

Since all signal processing and quantification steps are usually run through during post-processing of MRS data, the determination

of a lower cut-off is suitable for reliable detection. Depending on the examination and the acquisition sequence, concentrations between 0.897 mM [21] and 1.8 mM [22] and a ratio to creatine of 0.11 [38] have been reported.

In a meta-analysis of 14 scientific publications with a total of 460 treatment-naive patients, Suh *et al*. [12] reported a pooled sensitivity of spectroscopic 2-HG detection of 95 % (95 % confidence interval CI, 85–98 %) with a specificity of 91 % (95 % CI, 83–96 %). It must be taken into consideration here that the detection reliability is significantly lower in patients already treated with chemotherapy or neurosurgery. In a recently published study, Di Stefano *et al.* [37] showed a reduction in sensitivity from 95 % to 62 % in treated patients – due to the smaller tumor volumes and the consequently unfavorable voxel coverage (partial volume effect).

De la Fuente *et al.* [39] were able to show a relationship between the sensitivity for 2-HG detection with the voxel volume for PRESS. For volumes < 3.4 mL, 2-HG was able to be detected with spectroscopy in only 8 % of measurements (2 of 24) in patients with IDH-mutated gliomas but in 20 of 22 cases (91 %) for volumes ≥ 8 mL. The study by Di Stefano *et al.* [37] highlights this with a highly significant relationship ($p < 0.001$) between 2-HG detection with MEGA-PRESS and the achieved voxel coverage.

Compared to immunohistochemical detection or genomic sequencing, Suh *et al.* [40] report a false-positive rate of 2-HG detection of 21 % in glioblastomas. There was a relationship between necrotic tissue in the examination volume and the false-positive rate. As a result of the high concentration of lipids in this tissue, signals between 2.0 ppm and 2.9 ppm that can simulate the 2-HG resonance at 2.25 ppm can be seen. By using editing techniques (MEGA), this can be avoided as shown by Branzoli *et al.* [27]. MEGA-PRESS proved to be the better acquisition method for both the detection and the determination of the concentration of 2-HG (compared with concentrations determined analytically by gas chromatography with mass spectrometry coupling).

Clinical significance

The new classification of tumors of the central nervous system published in 2021 by the World Health Organization (WHO) increasingly integrates molecular genetic changes. Detection of mutations in the genes of isocitrate-dehydrogenase (IDH) and the chromosomal loss of 1p and 19q are decisive here [1]. An IDH mutation is typically detected by neuropathological workup of tumor tissue acquired by biopsy or microsurgical resection. Reliable spectroscopic detection of 2-HG could provide initial diagnostic and prognostic information. This is particularly true for the differentiation between nonspecific incidental brain lesions and IDH-mutated gliomas. Finally in the case of high suspicion of an IDH-mutated glioma, surgical resection or, if not possible for functional reasons, biopsy is performed and adjuvant treatment is initiated if a tumor is detected [41].

Moreover, there are studies examining the concentration dynamics of 2-HG during monitoring of ongoing tumor treatments [42]. This form of treatment monitoring can be highly relevant particularly for future molecular treatments with IDH inhibitors [43]. However, reliable detection and quantification require prior experience with the method so that it is best implemented at facilities with corresponding spectroscopy expertise.

The differential diagnosis must take into account that 2-HG also occurs in the rare congenital condition 2-hydroxyglutaric acidemia [44]. A significantly elevated 2-HG concentration in the urine and CSF has been observed in this condition [45].

Conclusion and outlook

MR spectroscopic detection and quantification of 2-hydroxyglutaric acid provide radiology with an effective method for expanding morphological characteristics from MR imaging to include relevant metabolic information in the case of brain tumors. With acceptable acquisition times, *single voxel spectroscopy* can provide additional information, thereby facilitating both the diagnostic process as well as the prognostic counseling of patients with previously unclear brain lesions [43]. Due to the weak and split MRS signal of 2-HG, high data quality, good shimming, and an adequate SNR are required. This is not always the case under clinical conditions. In particular, the measurement of already treated gliomas is challenging and sometimes not possible due to necrotic tissue, large susceptibility differences, CSF in the resection volume, or an insufficient (residual) tumor volume. Editing techniques (MEGA) allow targeted adaptation to the resonance and coupling pattern of the metabolite and thus seem to be the more specific method, compared to non-editing methods, especially at a field strength of 3 Tesla. However, this technique – as already mentioned – has some limitations due to the sensitivity to inhomogeneous measurement conditions and the need for longer acquisition times and larger measurement volumes. The main challenge regarding the spectroscopic measurement of 2-HG is the provision of a protocol that is adapted to the clinical question and the present measurement conditions and the ensuring of competent data post-processing and quantification.

With a highly significant relationship between cystathionine (Cystat) and a 1p/19q codeletion in IDH-mutated gliomas, Branzoli *et al.* [24] were able to call attention to another possibly oncologically significant metabolite. Thus, MR spectroscopic differentiation based on 2-HG (IDH mutation vs. IDH wild type) could be expanded in the future to include an additional differentiation criterion defined in the WHO classification (1p/19q codeletion vs. 1p/19q intact). The consequently possible noninvasive differentiation of an IDH-mutated oligodendroglioma from an IDH-mutated astrocytoma again shows the great potential of MR spectroscopy as a "virtual" biopsy method. ▶ **Fig. 2** shows the position of the detectable cystathionine resonance. Thus, the oligodendroglioma identified in this case by neuropathological workup can be confirmed by MR spectroscopy.

Conflict of Interest

The authors declare that they have no conflict of interest.

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