Case Report

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Tumefactive Demyelinating Lesions in Multiple Sclerosis: Role of Magnetic Resonance Spectroscopy (MRS)

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Abstract

Tumefactive Demyelinating Lesions (TDL) is characterized by large demyelinating lesions that frequently mimic intracranial neoplasm or abscess. Proton Magnetic Resonance Spectroscopy (MRS) imaging is a potentially exciting tool to help in the diagnosis. Literature reports, studying the potential utility of MRS in differentiating TDLs from neoplasms, have focused on the quantification of biochemical metabolites such as *N*-acetyl aspartate (NAA), Choline (Cho), Creatine (Cr), Lactate (Lac), mobile Lipids (Lip) and Glutamate (Glx). We hereby report MRS findings of three patients with tumefactive lesions, i.e. elevated Choline and Lactate (except patient 3) peaks with reduced NAA peaks, consistent with demyelination. Based on the improvements in clinical and imaging outcomes during subsequent follow ups confirming Multiple Sclerosis (MS), we propose that elevation of Lactate and Choline peaks together with reduction of NAA peak on MRS study together with clinical picture may serve as an important non-invasive tool to differentiate TDL from other radiological correlates.

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Introduction

To present three patients with Tumefactive Demyelinating lesions on MRI brain, later diagnosed as definite Multiple Sclerosis (MS), and the findings of Magnetic Resonance Spectroscopy (MRS) imaging with review of literature. Tumefactive Demyelinating Lesions (TDL) is large demyelinating lesions that frequently mimic intracranial neoplasm or abscess on conventional MRI. MRS is an exciting non-invasive radiological tool to help in the diagnosis.

This is a descriptive case series of three patients who presented to us with focal neurological deficits (age range; 24-37 years, M:F-2:1). These were either diagnosed MS cases who subsequently developed parenchymal mass lesions (patient 1 &3) or revealed a tumefactive lesion on their first encounter (patient 2). Combined MRI/MRS studies were performed on a 1.5T "Siemens Skyra combined imaging and spectroscopy system" imaging unit with a standard head coil. Multi-voxel quantitative proton MR spectroscopy sequences were obtained utilizing a point-resolved spectroscopy sequence protocol with a short spin echo time of 135 milliseconds (ms). Image-guided selection of a Region of Interest (ROI) for proton MRS was based on T1-weighted fast-low-angle-shot images.

Conventional MR images included T1-and T2-weighted Images (T1WI, T2WI), Fluid Attenuated Inversion Recovery (FLAIR) images, post-contrast T1-weighted images, as well as diffusion weighted imaging (DWI) with corresponding apparent diffusion co-efficient (ADC) values. Peak heights of N-acetyl Aspartate (NAA), choline (Cho), and Creatine (Cr) were measured. Cho/Cr and NAA/Cr ratios of corresponding regions in TDLs were measured. Lactate peaks were noted.

Case Report

Patient 1

A 24-year-old male with history of quadriparesis in 2010 that responded to 5 days of human immunoglobulins (IVIG), presented in September 2017 with paresthesia of all four limbs that resolved completely after steroid pulse therapy (IV Methylprednisolone for 5 days). MRI spine and brain showed lesions consistent with MS. Cerebrospinal Fluid (CSF) analysis were positive for Oligoclonal bands. Disease modification therapy was initiated with Teriflunomide, Betaferon (interferon beta-1b) followed by

Dimethyl fumarate, adjusted in accordance with the patient's tolerability and clinical profile. Disease progression however, continued despite disease modifying therapy, both clinically and radiologically. He later presented with mild visual disturbance with numbness in left face and lower limb. MRI brain revealed increased number of the hyperintense foci in both cerebral hemispheres, many showing contrast enhancement, with a larger lesion in the left centrum semi ovale with no significant peri-focal edema. MRS showed evidence of elevated peaks of Cho and Lac with mild reduction of NAA consistent with demyelination or TDL (**Figure 1**). Therapy was then escalated to Ocrelizumab. He improved and remained relapse-free afterwards (Extended Disease Stability Score- EDSS 0). Follow up MRI scan, a year later, showed regressive course of the disease.

Patient 2

A 32- year-old male who was seen in June 2018 for sub-acute progressive right lower limb weakness, numbness over left lower limb up to umbilicus and gait impairment (EDSS 3.0). He had history of urinary symptoms, imbalance, dizziness, ataxia and excessive fatigue over the preceding 3 years, each lasting for more than 24 hours and never associated with any febrile illness. Examination was significant for right leg weakness (3/5 on Medical Royal College scale), bilateral lower limb hypoesthesia up to mid-thigh in right leg, and sensory level up to T10 on the left side. CSF analysis was normal. MRI brain and spine was consistent with diagnosis of MS along with a left frontal lesion for which MRS was done which revealed elevated Lac and Cho peaks along with reduced NAA peak, changes consistent with TDL (**Figure 2**). He received IV Methylprednisolone for 5 days and his symptoms improved markedly. He was later started on Cladribine. He showed good clinical response with the only complain being feeling tired after a long walk. Repeat MRI brain revealed resolution of lesions.

Patient 3

A 37-year- old female, known to have MS since 2003, on Fingolimod since 2014 with impaired visual acuity in the left eye, mild right lower limb weakness and slight impairment in tandem walk (EDSS 2.5) developed a new relapse (progressive burning sensation from feet up to the thoracic area, urinary retention and

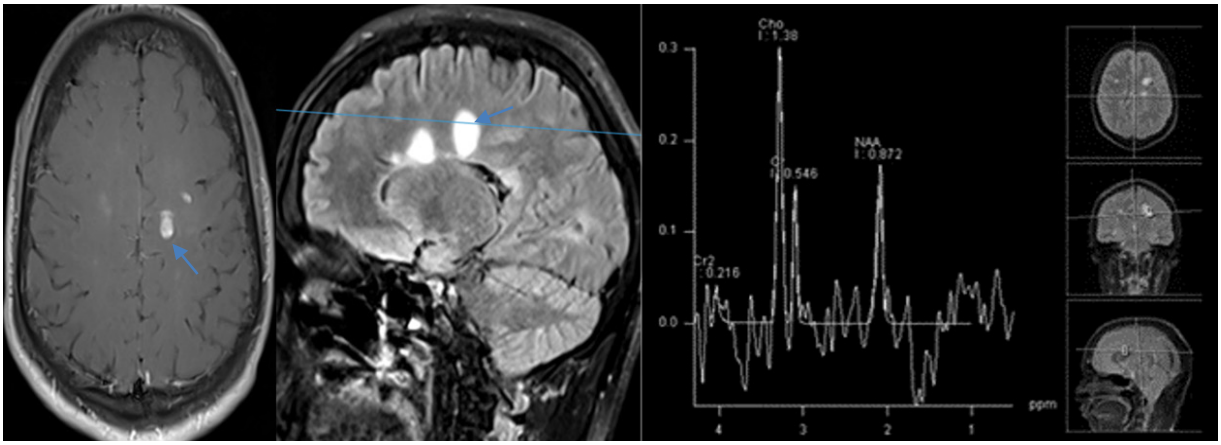

Figure 1 TIWI contrast axial, FLAIR sequence sagittal images showing lesion in the left centrum semi ovale measuring up to 1.9 × 1.6 cm with gadolinium-enhancement but no significant perifocal edema. MRS at the level of lesion showing elevated peaks of choline and lactate with mild reduction of NAA.

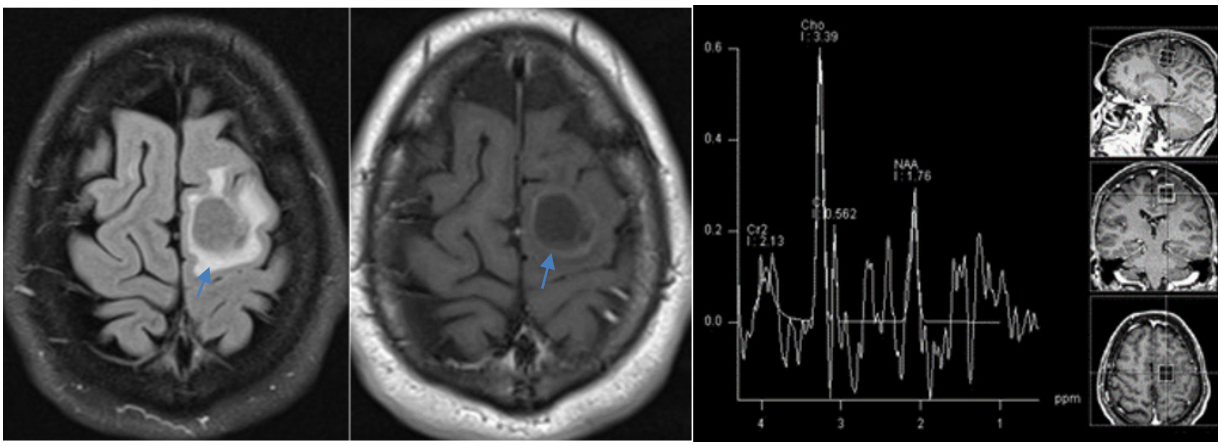

Figure 2 FLAIR- and TI- contrast axial images showing lesion in left frontal centrum semi ovale measuring 2 cm x 2.5 x 4 cm, hypointense in FLAIR surrounded by perifocal edema, mass effect and faint rim enhancement. MRS showing elevated lactate and choline peaks while NAA peak is reduced.

lower limbs weakness, EDSS 3.5) (**Figure 3**). MRI brain showed a left parietal cystic lesion with no contrast enhancement along with other additional lesions consistent with MS. MRS of the cystic lesion showed relatively low NAA and high Choline peaks, suggestive of TDL. She did not show much improvement on steroid pulse therapy, hence IV Immunoglobulins was instituted to which she responded well. She was subsequently switched to Natalizumab which she tolerated well and remains relapse free for following three years.

Discussion

Multiple Sclerosis (MS) is an autoimmune disease of the Central Nervous System (CNS) characterized by areas of inflammation, demyelination and degeneration, largely affecting young patients with a relapsing-remitting or progressive clinical course [1].

The so-called Tumefactive Multiple Sclerosis (TMS) with large TDL on imaging is a rare entity. Conventional MRI may not help much to differentiate TDL from primary brain neoplasm or abscess. These TDLs can either be solitary or multiple characterized by large demyelinating plaque sized ≥2 cm and associated with variable presence of perilesional edema, involvement of gray matter structures and post-contrast enhancement, typically open-ring enhancement facing the cortex [1-3]. Some other MRI findings suggesting demyelination include a hypointense rim on T2WI, little mass effect or vasogenic edema, primarily involvement of white matter, central dilated vein within the lesion, involvement of corpus callosum, peripheral ADC patterns at the lesion edge with significant peripheral diffusion restriction, and possible lesion regression after appropriate therapy. Despite this, especially in the event where a patient presents with first neurological event and a solitary lesion on routine imaging, the diagnosis may get challenging [4,5]. Notably, in suspected TMS, additional testing like CSF analysis for Oligoclonal bands may not add much as it is positive in just ~30% of patients with TMS [6]. In difficult cases, therefore, histopathological diagnosis might appear as the only answer to get a definite diagnosis. Hence, arise the need to have some non-invasive testing which can help to secure the diagnosis and save these patients from unwarranted invasive procedures, treatment delays and undesirable prognosis of a potentially treatable disease.

Proton MRS is a non-invasive analytical tool to help delineate suspected TDL/TMS lesions from other possible etiologies. Additionally, it can be implemented on most conventional high-field MRI scanners making its availability almost universal.

Bottomley PA, et al. [7] published the first human *in vivo* solvent-suppressed proton spectrum of the brain in 1985. Since then, there are increasing reports addressing the role of MRS in differentiation of demyelinating and intra-cranial neoplastic lesions by assessing the biochemical metabolite status in both.

By far, most spectroscopy studies use the proton (^{1}H) nucleus, because of both its high sensitivity and ease of implementation on commercial MRI scanners. The technique acquires information about protons from molecules other than water. Two important metabolite peaks that are routinely quantified on the ^{1}H-MR spectrum of tissue from the human CNS are total methyl resonance of N-acetyl-containing compounds (tNA) that resonate at 2.01 ppm relative to the standard tetramethylsilane and total methyl resonance of Cr and phosphocreatine (tCr) that resonates at 3.03 ppm. Present in abundance in adult mammalian brain, the tNA peak primarily reflects the presence of N-acetylaspartate (NAA) which is synthesized by neuronal mitochondria, and along with Glutamate, is involved in cell-specific signaling between neurons, astrocytes and oligodendrocytes. Because of the presence of its constituent-metabolites in neurons and its prominence in the ^{1}H-MR spectrum, tNA peak serves as a marker of neuronal loss in a variety of CNS diseases, including demyelination like MS [8]. The tCr peak reflects the presence of Cr and phosphocreatine, molecules engage in energy metabolism, with the later representing reserves of high-energy phosphates that provide for homeostasis and energy needs. Additionally, tCr peak is present in both neurons and glial cells, with highest concentration in astrocytes and oligodendrocytes [9].

The spatial localization techniques for MRS are either single-

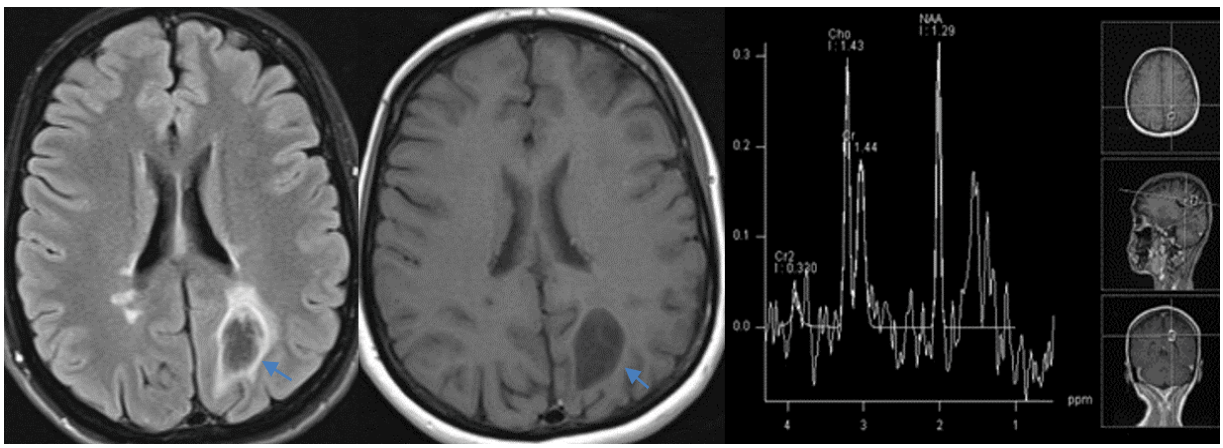

Figure 3 T2WI -and T1WI -contrast axial images showing a left parietal cystic lesion with mild perifocal edema and no contrast enhancement. MRS showed relatively low NAA and elevated choline peaks.

voxel techniques (recording spectra from one region of the brain at a time) or multi-voxel techniques (simultaneous recording of spectra from multiple regions) typically performed in 2- or 3-dimensions and thereby mapping out the spatial distribution of metabolites within the brain [10].

Proton MRS (^{1}H-MRS) provides biochemical information in not only visible lesions on conventional MRI but also in Normal Appearing White Matter (NAWM). This has led to insight into dynamic regional biochemical alterations in demyelinating plaques as seen in serial longitudinal studies. The biochemical abnormalities found on MRS with normal corresponding MRI in demyelinating diseases have demonstrated that- a) the axonal damage may occur at early stage, b) the neuronal loss can be substantial in the gray matter; and c) widespread biochemical involvement may be detected earlier on MRS. Moreover, the extent of neuro-axonal involvement has been shown to significantly correlate with neurological dysfunction, thus implicating a beneficial role in clinical monitoring [11].

The development of single-voxel techniques allowed quantification of the absolute concentrations of metabolites that are readily observed in 1H spectra, which in addition to NAA and tCr, include Lactate (Lac), amino acids, inositols, and choline-containing compounds. Previous MRS reports have described NAA reductions as a main feature of demyelinating as well as other neurometabolic disease [12]. These biochemical spectra on 1H-MRS also point towards potential therapeutic targets in MS, e.g. NAA peak changes suggesting early neurodegeneration led to a reconsideration of the role of axonal damage in MS while changes in metabolites such as choline and myo-inositol(mIns), established the importance of assessing myelin damage and repair [13].

These metabolite concentrations tend to vary in different diseases due to the variations in the underlying pathophysiology such as axonal and myelin damage, peripheral proliferation, necrotic core, edema etc. Pathologically, TDL are indistinguishable from a typical MS plaque. A typical acute White Matter Lesions (WML) in MS is characterized by breakdown of the blood-brain barrier and focal area of inflammation with dense perivascular inflammatory infiltrate that contributes to demyelination and axonal degeneration with oligodendroglial loss and reactive gliosis (i.e. astrocytic proliferation) [14]. A TDL is characterized by infiltrating foamy macrophages intermingled between reactive astrocytes and possible accumulation of lipid within the plaque due to myelin breakdown. Some pathological studies have demonstrated the presence of axonal injury as well [15].

MRS showing elevated level of choline-containing compounds (result of reactive astrogliosis, inflammation and release of choline-containing membrane lipids during active myelin/cell membrane breakdown) along with reduced NAA levels (result of neuronal destruction, axonal damage, and neuronal mitochondrial dysfunction) are common finding in the acute MS lesion with or without increased lactate from inflammation. Abnormally elevated lipid and mIns peaks may also be observed on short TE MRS Sequences. Importantly, choline-containing compounds and lactate may return to normal overtime but NAA does not recover back to normal [16,17].

Bitsch A, et al. [17] studied metabolic-pathological correlates in 3 patients (2 diagnosed later as clinically definite MS (CDMS), 1 remained undiagnosed without any further clinical event) who underwent combined 2-T MR/MRS studies (T1-weighted fast low-angle shot and single-voxel stimulated-echo acquisition mode) along with simultaneous acquisition of same from a group of 40 age-matched healthy volunteers. They observed parallel decreases of NAA with reduced axonal density in demyelinating plaques while concomitant increases of Cho and mIns were seen with corresponding glial proliferation. Furthermore, marked Cho increase was seen in inactive lesions with fibrillary gliosis while elevated Lac was found to be associated with inflammation. All MRS examinations of biopsied lesions exhibited marked increases of the absolute Cho (75%–152%) and Ins (84%–160%) levels.

Husted CA, et al. [18] studied 13 patients with CDMS with 19 controls. They analyzed metabolite changes in MS plaque, MS-NAWM, and region-matched control spectra from the centrum semiovale. Moreover, they also measured the phospholipid metabolites in such lesions using phosphorus (31P) MRS imaging. MS patients underwent both ^{1}H MRS and 31P MRS, while controls had either of the two or both. The authors observed that the metabolite ratio NAA/Cr and the total 31P peak integrals were significantly reduced in both WML and NAWM in patients with MS. NAA/Cho and phosphodiesters/total 31P ratios were found significantly reduced in MS lesions, along with a trend towards reduced NAA/Cho in MS-NAWM. In MS-NAWM, tCr and phosphocreatine were significantly increased. The authors attributed these changes to reduced neuronal density and altered phospholipid metabolites in WML in MS patients.

Histopathological studies of NAWM as seen on conventional MRI have been shown to have pathological changes depicting neuroaxonal disturbance [19]. These biochemical changes are liable to type and severity of pathological processes (e.g. chronic demyelination and gliosis, acute inflammation and demyelination), therefore, the spectroscopic findings may change over a period of time.

Arnold DL, et al. [20] did serial MRS in a patient with biopsy-proven MS and reported elevated Lac and Cho signals at 3 days after the onset of symptoms with a reduced NAA signals a few days afterward. While Cho (outside the lesion) and Lac (everywhere) signals notably returned back to normal, there was no recovery of NAA signals in or adjacent to the lesion on MRI. The authors proposed abnormal Cho signal as indicator of recent regional demyelination, with persistent abnormal signals from NAA as an index of irreversible neuronal damage.

Another longitudinal study (25 MS patients and a total of 124 MR Sessions scanned at varying intervals for up to 2 years) showed appearance of metabolic changes for some patients ahead of appearance of lesions on conventional MRI. The authors found: a) metabolite level changes being dynamic and reversible in some patients, b) an inverse correlation between the average NAA within the spectroscopic volume and the total lesion volume in

the whole brain suggesting NAA use as an objective marker of the disease burden, and; c) elevated Lipid peaks in 4 patients in the absence of Gadolinium enhancement and MRI-defined lesions suggesting demyelination occurring independent of perivenous inflammatory changes. Interestingly, due to transient changes in NAA levels in acute plaques, the authors concluded that a reduced NAA level does not necessarily imply axonal loss [21].

The studies addressing spectroscopic findings particularly in TDL remain far and between. De Stefano N, et al. [22] reported the MRS findings in 4 patients with a single large demyelinating plaque who were followed for variable period of time (7 months to 3.5 years). They observed increased relative resonance intensities of Choline-containing compounds, Lac and mIns inside the acute lesion with decreased relative resonance intensities of NAA and Cr both in and around the MRI-detected lesions. Follow up showed reduced Cr, Lac, and mIns resonance intensities. While choline compounds showed slow and variable recovery, all patients showed partial recovery of the NAA resonance intensities. They also observed significant negative correlations between NAA resonance intensities and both brain lesion volumes and clinical disability.

Another report on 3 patients with TDL, observed normalization of initial increases in lipid and lactate peaks within three to four weeks, followed by persistent, marked reductions of the NAA and magnetization transfer ratio values around or below 30%, a histological correlate of marked demyelination in the absence of significant inflammation. [23].

Saini J, et al. [24] reviewed conventional MRI and multivoxel ^{1}H MRS findings in 18 patients with demyelinating lesions; 9 being biopsy proven. They also compared these findings with Diffusion Tensor Imaging (DTI) in 15 patients. Various metabolite ratios were calculated at different depths of the demyelinating lesions at TE 135 ms. The central part showed variable Cho and significantly low NAA. The intermediate area showed higher Cho and lower NAA compared to contralateral normal side. The outermost layer, corresponding with the contrast enhancing areas on MRI, showed high Cho, lower NAA, and restricted diffusion on DTI. The authors observed increased Glutamate and-glutamine (Glx) in tumefactive lesions along with Lac which appeared higher at the center compared to the periphery of lesions. While the conventional MRI showed shrinkage of index lesions with disappearance of contrast enhancement and diffusion restriction, MRS abnormalities remained persistent on follow-up imaging. The authors concluded that TDLs have different microstructural changes at different depths of the lesion, a quality which can be useful in differentiating these lesions from others [24].

Wattjes MP, et al. [25] studied 3T whole-body MRI and single-voxel ^{1}H-MRS findings (TE: 38 ms and 140 ms) of the parietal NAWM in demyelinating disease [36 patients with clinically isolated syndrome (CIS), 12 patients with MS, 20 normal controls]. They found that mean NAWM mIns concentrations were significantly elevated in the MS group but not in the CIS group. The higher concentration of mIns in the MS group was also reflected in the significantly increased Ins/tCr ratio. The mean NAWM tNAA was significantly decreased in both CIS and MS compared with the control group. In the light of these findings, the authors concluded that the significant increase of the activity of the glial cells can only be observed in patients with an established diagnosis of MS but not in patients with CIS. They also conferred that the patients, in both CIS and definite MS groups, already have axonal damage during the first demyelinating episode.

Using single voxel MRS, Tisell A, et al. [26] compared the spectroscopic findings in NAWM and thalamus in patients with CDMS with healthy controls (n=20). The MS patients were labelled as atypical MS/MRI negative (MRIneg) if they had two or fewer lesions on MRI (n=15), or typical MS/MRI positive (MRIpos) if the lesion load was higher (n=20). Their observations revealed higher concentrations of glutamate and glutamine (Glx) in both MS groups (MRIneg 8.12mM and MRIpos 7.96 mM) *vs*. controls, 6.76 mM. They also observed lower NAA and N-acetylaspartate-glutamate (tNA) and elevated mIns concentrations in NAWM of the MRIpos patients as compared to both controls and MRIneg. The authors concluded that a) NAWM Glx levels may serve as an important pathological marker in MS, b) Glx is related to the severity of MS independent of number of lesions in the patient, and c) increased glial density as indicated by increased mIns and decreased neuronal density as indicated by the decreased tNA, were only observed in NAWM of typical CDMS patients with WML.

Gustafsson MC, et al. [27] compared 14 CDMS patients with normal MRI and the spectroscopy findings with healthy controls (n=14). Using 4-voxel ^{1}HMRS, they found significantly lower concentration of N-acetyl compounds (tNA), including NAA and N-acetyl aspartylglutamate as well as lower choline-containing compounds (Cho) in patients with MS compared with healthy controls. They also described a positive correlation of EDSS to mIns concentrations as opposed to negative correlation to tNA concentrations.

A meta-analysis addressing the techniques used and the spectroscopic findings obtained in patients with MS as compared to healthy controls suggested that within-voxel tNA/tCr ratios can be interpreted as valid and accurate surrogate measures of 'cerebral tissue integrity' -with decreased tNA/tCr ratios indicating some combination of neuroaxonal disturbance, oligodendroglial disturbance, and astrocytic proliferation. It was also noted that although within-voxel tNA/tCr ratios are not perfect indicators of tNA content, they do represent a practical compromise to acquiring surrogate measures of within-voxel neuroaxonal integrity [19].

Intra cranial neoplasms are a major differential to TDL and may pose a diagnostic challenge as the patients usually present with first neurological event, the MRI may show solitary or multiple lesions with confounding imaging findings; and may share similar spectroscopic spectra due to similar pathological features with other diseases. While there is ample literature addressing spectroscopy and its role in brain tumors, little is known about role of MRS in differentiation of demyelinating lesion from brain tumors.

Table 1 Summary of findings on MRI and MRS brain.

Patient	Age (year)/ Gender	Known MS	TDL (n)	Gadolinium Enhancement	Lactate Peak	Choline Peak	NAA Peak	Lesion Resolution on Follow Up
1	24/Male	Yes	1	Present	Elevated	Elevated	Reduced	Present
2	32/Male	No	1	Present	Elevated	Elevated	Reduced	Present
3	37/Female	Yes	1	Absent	Not elevated	Elevated	Slightly reduced	Partial only

A neoplastic spectroscopic profile generally includes the following: an attenuated NAA peak, consistent with neuronal loss; an elevated Cho resonance indicating increased turnover (synthesis and/or degradation) of cell membrane and myelin components; an attenuated Cr peak reflecting depressed cellular energetics and/or cell death from lesional necrosis; and variable Lipid and Lac peaks indicating areas of cellular necrosis with the release of free lipids and anaerobic metabolism with lactate production as a by-product [28].

Their metabolic inhomogeneity results in overlaps in generally seen decreased NAA/Cr ratio, increased Cho/Cr ratio, and variable presence of Lac and Lip in both entities.(5-8) Proton MRS has been implicated for non-invasive monitoring of treated brain tumors, in assessing tumor-grading, tumor- recurrence, differentiating tumor recurrence from radio-necrosis; and recently in prediction of molecular subgroups as well [29,30].

The work by Fulham MJ, et al. [31] revealed generally decreased NAA in tumors and radiation necrosis with some degree of preserved levels at neoplasm margins; generally increased Cho in most solid tumors, especially high-grade gliomas; lower Cho values in necrotic high-grade lesions, chronic radiation necrosis and following therapy; and likelihood of Lac in high-grade gliomas. However, the authors concluded that due to reduced Cho in necrotic high-grade lesions, neither the normalized choline value could discriminate the tumor grade, nor the presence of lactate any reliable indicator of malignancy.

With 176 intracranial lesions, mostly histologically verified, who underwent 1.5-T single-volume ^{1}HMRS following structural MRI and/or CT imaging, Hartman et al were able to determine that the additive information of 1H-MRS led to a 15.4%-higher number of correct diagnoses, 6.2% fewer incorrect and 16% fewer equivocal diagnoses than with structural MRI data alone. However, the cohort did not include any demyelinating lesion and so the findings could not be compared with the later [32].

Using volume selective MRS (stimulated echo acquisition mode (echo time, 20 and 270 ms) and spin echo (echo time, 135 ms) sequences, Poptani H, et al. [33] reported high Cho and low or absent NAA and Cr along with lipid and/or Lac in high-grade gliomas (n=37) while low-grade gliomas (n=23) showed low NAA and Cr and high Cho and presence of Lac alone. The same resulted in significantly lower NAA/Cho ratio and a higher Cho/Cr ratio in high-grade gliomas. The authors noted that the presence of lipids suggested a high grade tumor and concluded that NAA/Cho ratio, Cho/Cr ratio and presence of lipids when combined can be helpful in grading of gliomas.

Shimizu H, et al. [34] compared the single-voxel point resolved spectroscopy findings from the frontal white matter in patients with brain tumors (n=25) with controls (n=17). Higher Cho/reference value and lower NAA/reference values were associated with high-grade gliomas.

Birchall DJ, et al. [35] reported a patient whose initial MRS demonstrated elevated peaks of Cho, Lac and lipid, along with reduced NAA peak, a pattern suggesting either a low grade glioma or an acute demyelinating plaque. A follow up study 4 months later revealed same spectroscopic pattern, later followed by a histopathological diagnosis of oligodendroglioma.

Another report compared conventional MRI and multi-voxel MRS findings in patients with TDL (n=6) with high-grade glioma having similar MRI findings (n=10). They found no significant differences in mean Cho/Cr ratios in the corresponding contrast-enhancing, central, or perilesional areas of TDLs and gliomas. There was significant lower mean central region NAA/Cr ratio in case of gliomas but mean NAA/Cr ratios in other regions were not significantly different. A Lac peak was identified in 4/6 (66.6%) TDLs and 3/10 (30%) of gliomas. The authors noticed that the overall metabolic profiles of both lesions were similar emphasizing the need for the cautious interpretation of spectroscopic findings [2].

Ryotaro I, et al. [36] studied two cohorts of patients with TDL and gliomas [cohort 1 using a 1.5T MR unit: TDL (n=6) and glioma (n=5, high-grade in three patients); cohort 2 using a 3.0T MR unit: TDL (n=6) and glioma (n=17, high-grade in eight patients)]. Patients underwent single-voxel proton MRS to assess the following metabolite area ratios: Cho/ Cr, NAA/Cr, and Cho/NAA in both cohorts. In addition to this, 15 patients from cohort 2 (four with TDL) also underwent methionine-positron emission tomography (MET-PET). The authors found that as compared to TDL, the mean Cho/NAA ratio was significantly higher in gliomas in both cohorts. They also estimated that high-grade glioma was indicated when the Cho/NAA ratio was >1.72, suggesting Cho/NAA ratio as predictor of high-grade glioma. Additionally, a significant positive correlation was observed between Cho/NAA ratio and the MET-PET ratios.

Some other studies observed an abnormal elevation of the Glutamate/Glutamine (beta & gamma Glx) peaks in tumefactive lesions, a finding that may not usually be seen in the aggressive intra-axial neoplasms. One such report presented 4 patients with biopsy-proven MS and tumefactive lesions, who underwent single-voxel MRS utilizing a point-resolved spectroscopy sequence protocol with a short echo time (30 ms). The spectroscopic pattern revealed significant elevation of the Glx peaks (2.1–2.5 ppm) along with elevated Cho peak (3.2 ppm), elevated Lac peak (1.3 ppm), elevated lipid peak (0.5–1.5 ppm), and concomitant decrease in the NAA peak (2.0 ppm) [37].

Malhotra HS, et al. [38] studied conventional MRI and MRS findings

in 18 patients with TDL and reported that 9/18 (50%) patients showed glutamate/glutamine (Glx) at 2.4 ppm. The authors concluded that clinical features, MRI characteristics suggesting demyelinating disease and presence of Glx on spectroscopy when put together may be rewarding in differentiating TDLs from neoplastic lesions.

Depending upon molecular subgroups as defined by the *IDH1/2* mutation and 1p19q-co-deletion, Diamandis E, et al. [30] found that Cho (in IDH wild type tumors like gliomas and astrocytomas); Cr and Glutamate (in IDH mutated tumors); and Lac were generally increased in contrast enhancing tumors while metabolites nNAA and nCho showed the strongest difference between normal appearing matter and tumor regions. They also noted high intensities of lipids in necrotic regions while high intensities of Cr were seen in the FLAIR hyperintense regions, potentially marking the infiltration zone of glioma [30].

Our patients had clinical and radiological findings fulfilling McDonald criteria and showing remarkable response to disease modifying therapy with significant clinical and radiological regression of disease. All 3 had MRI brain showing a large solitary lesion suspected to be tumefactive in origin, hence MRS was done which showed elevated Cho peak, elevated Lac peak (except patient 3) with reduced NAA peak, consistent with TDL (as summarized in **Table 1**).

Based on the clinical and imaging outcomes during subsequent follow ups and MRS findings, we conclude that elevation of lactate and choline peaks together with reduction of NAA peak were suggestive of demyelination, and may serve as a reliable indicator in case of TDL especially with a supportive clinical and conventional MRI data.

The available literature with heterogeneity in the study designs, variable time of imaging and lack of histopathological data, however, is still insufficient to provide a definite guideline regarding use of MRS in clinical practice as a definite diagnostic tool. More studies involving larger patient groups and standardized protocols would be advisable before the clinical utility of the technique can be fully evaluated.

Conclusion

Together with clinical profile and conventional Magnetic Resonance Imaging (MRI), proton MR spectroscopy utilizing cerebral biochemical substrate quantification may serve as a helpful non-invasive diagnostic tool in delineating tumefactive brain lesions. The level of confidence in its individual ability to differentiate TDL from neoplasms, however, remains debatable till date. Further studies using a unified MRS protocol and large cohorts of MS patients would serve to improve the confidence in MRS in delineating TDL, thus dictating a better and timely management without the need of invasive procedures.

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