

MRS in Stroke, MS and Infectious Disease

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Introduction

Although the main clinical application for magnetic resonance spectroscopy (MRS) is currently in the diagnosis and evaluation of treatment response of neoplastic lesions of the brain, there are also potential applications in other neurological disorders such as stroke, multiple sclerosis (MS) and infectious diseases. Radiologists who interpret brain spectra should certainly be aware of the metabolic consequences of ischemia, demyelination and infectious processes in the brain. This presentation will review the metabolic changes associated with each of these conditions, and also highlight instances where MRS may be of clinical use.

MR Spectroscopy in Stroke

As cerebral blood flow (CBF) decreases, various processes related to cerebral homeostasis gradually fail (1). Once CBF has decreased below 15 to 20 ml/100g/min (2), the brain becomes ischemic, with the cessation of electrical function, and the switch of energy metabolism from aerobic pathway (oxidative phosphorylation) to anaerobic glycolysis with accumulation of lactate (Figure 1). Reported CBF thresholds may vary depending on the animal model used, the type of anesthesia, the type and duration of ischemia, arterial oxygenation and hematocrit, and the method used to measure CBF. However, in complete, global ischemia induced by cardiac arrest, lactate levels rise abruptly (3) and reach a steady state within 10 minutes of cessation of blood flow. As lactate accumulates, the tissue may become acidotic (2). The "final" lactate concentration depends on a number of factors, but in particular on the pre-ischemic blood glucose and brain glycogen stores (3). Under normo-glycemic conditions, lactate may typically reach 10 to 12 mM (4). Pre-ischemic hyperglycemia may increase final lactate concentrations, and worsen eventual clinical outcome. If ischemia is incomplete, or reperfusion occurs, blood flow continues to supply glucose to the tissue which, if sufficiently damaged, is unable to metabolize it aerobically, and extremely high lactate concentrations may result (5).

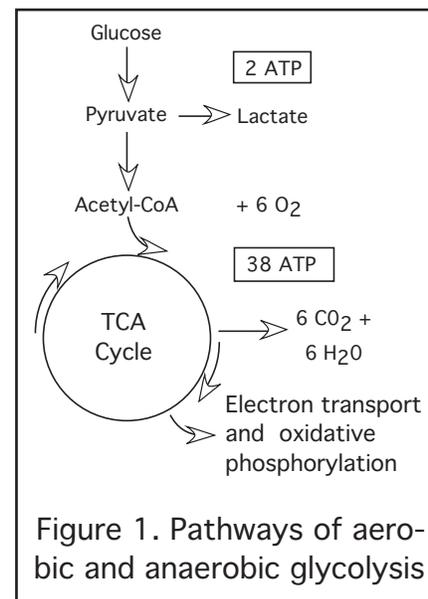


Figure 1. Pathways of aerobic and anaerobic glycolysis

In models of focal ischemia (where presumably CBF reductions are more moderate because of collateral circulation), the accumulation in lactate may often be significantly slower, increasing over a period of hours (6-9). For instance, in a permanent middle cerebral artery (MCA) occlusion model, lactate was observed to steadily increase up to 12 hours after induction of ischemia (8). In one report, it was also suggested that transient lactate elevations coincided with burst of cortical spreading depression (CSD) in peri-infarct tissue, which has been postulated to be a mechanism for infarct enlargement into surrounding tissues (9).

In addition to the increase in lactate, NAA is observed to decrease following the onset of ischemia. Several papers have described an initial rapid decrease in NAA of about 10% within the first few minutes (7,10,11) followed by a slower decline in NAA with a time constant of hours. The permanent MCA occlusion study of Monsein et al. (8) reported a 50% reduction of NAA in the basal ganglia within 6 hours of ischemia. The reason for an initial sudden drop in NAA followed by a slower decline is unclear, but it might indicate that either (a) two different pools of NAA exist, or (b) a decrease in some other compound which co-resonates with NAA at 2.02 ppm is occurring. It would appear that the rate of the subsequent, slower NAA decrease (like that of the lactate increase) is dependent on the degree of blood flow reduction to the ischemic tissue, but it is likely that the CBF thresholds for these processes are different, and that they also have different time constants. For instance, in both animal models of ischemia and in human stroke, elevated lactate in peri-infarct regions with near normal NAA levels has been reported (12,13). It is tempting to speculate that peri-infarct zone may represent an ischemic penumbra of dysfunctional tissue, with relative neuronal preservation, although at present this concept is largely untested.

If the duration (and/or severity) of ischemia is short enough (e.g. no more than a few minutes in the case of complete ischemia), then most of the metabolic alterations described above are reversible, i.e. establishment of reperfusion will result in restoration of normal metabolite levels and function (14). Reperfusion after a longer period of ischemia may result in initial restoration of metabolite levels, only to be followed by secondary energy failure over the subsequent 24-48 hours (7,15). As this secondary energy failure continues, or in the case of permanent ischemia, irreversible changes occur and the tissue will progress to neuronal loss, infarction and gliosis. These longer term changes can also be detected with MR spectroscopy; in the first two papers reporting MR spectroscopy of human brain infarction, NAA was completely absent from both infarcted tissue at 4 days (16) and at 10 months post stroke onset (17). As described above, other metabolic changes have also been reported in the chronic stage of stroke; these include increases of choline containing compounds (12) and mobile lipid signals (18).

The earliest studies of ¹H MRS of human stroke used single-voxel localization techniques (16,17). Using SV-MRS, it was found that elevated lactate and decreased N-acetyl aspartate (NAA) levels could be detected in cases of acute (<24 hours) (19-21), sub-acute (24 hours to 7 days) (16,21,22) and chronic (> 7 days) (17,19,22-24) stroke. While SV techniques have short scan times and are widely available, they do not however provide information regarding the spatial distribution and extent of metabolic abnormalities, and require that the location of the ischemic or infarcted region be already known or visible on MR Imaging (MRI) studies. There have, therefore, been efforts to develop spectroscopic imaging (MRSI) methods for the study of cerebral ischemia, either in one (25,26) or two spatial dimensions (27,28), or using multi-slice 2D MRSI (12,29).

An example of an acute stroke patient scanned using multi-slice MRSI is shown in Figure 2; the patient presented with a left hemiparesis as the result of a complete occlusion of the right internal carotid artery (ICA), and diminished flow in the right middle cerebral artery (MCA). Conventional T2-weighted MR images were normal. However, proton MRSI revealed elevated lactate throughout much of the right MCA territory, with the highest concentration in the basal ganglia (Figure 2A). NAA was mildly reduced in the right basal ganglia compared to the left. A follow-up MRI one week later showed a basal ganglia infarct but sparing of the cortical gray matter regions.

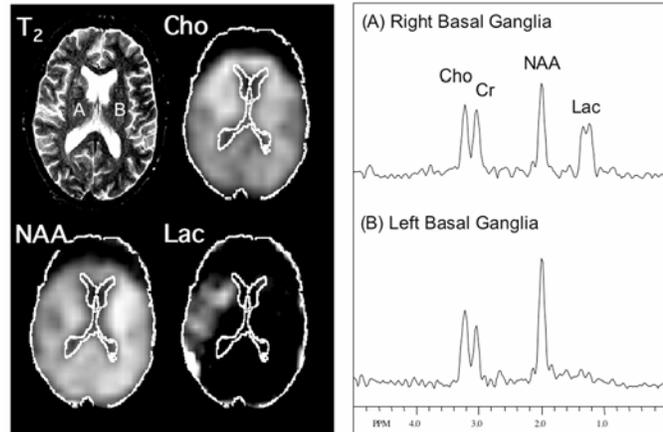


Figure 2. Proton MRSI in acute stroke

While the metabolic changes observed by MRSI are large and may provide information not available from other imaging modalities, there are currently few clinical applications for MRSI in acute stroke. This is partly because of the difficulty of performing MRSI in acute stroke patients, and also the availability of diffusion and perfusion MRI (DWI/PWI) with high spatial and temporal resolution. However, the observation of lactate may help distinguish ischemic lesions from others that may mimic strokes, although the specificity may not be particularly high, since lactate can also be found in some tumors and inflammatory lesions as well.

Potentially, MRSI could be incorporated into management decisions for patients with acute stroke, along with other imaging modalities such as DWI/PWI. For instance, a positive indication for thrombolysis might be the observation of a perfusion deficit, but still with high NAA levels indicating that infarction has not progressed too far. Another application (and perhaps more realistic, given the difficulty of performing MRSI in an acute setting) may be in evaluating patients with sub-acute stroke, or evaluating patients who may be eligible for other less urgent treatments such as carotid endarterectomy (CEA) (30). For instance, in one study (31), a low ipsilateral ratio of NAA/Cho in patients who had symptomatic carotid artery occlusion was found to be predictive of recurrent or further ischemic events, suggesting that this finding may be useful in deciding who should have CEA. In comparing patients before and after CEA, it was found that the NAA/Cho ratio improved post CEA, but only in patients who did not have lactate (in non-infarcted tissue ipsilateral to the occlusion) prior to CEA (32). These results and others indicate that proton MRS may be useful for both the selection of patients and monitoring of sub-acute stroke treatments, and in particular CEA.

There have been relatively few studies of the prognostic value of MRS in acute stroke. Pereira et al. found significantly lower NAA in patients who ultimately died or were dependent on others for their daily living activities, as opposed to those who were able to live independently, and the prognostic value was enhanced by combining NAA levels with acute infarct volumes on T2 MRI (33). Similar results have also been found by Federico et al. (34),

while Parsons et al. (35) found good predictive value based on acute measurements of lactate levels and lesion volume as detected by DWI. A recent study also found that elevated lactate levels in acute stroke patients with a PWI/DWI mismatch was predictive of subsequent infarct enlargement and poorer outcome than those with lower lactate levels (36).

Multiple Sclerosis (MS)

Multiple sclerosis is a chronic neurological disorder that affects the brain and spinal cord. The disease process, believed to be of autoimmune origin, involves inflammation, demyelination and axonal damage. Onset of MS typically occurs between the age of 20-50 years, is more common in women than men. The disease is characterized according to its clinical course as either relapsing-remitting (RR), secondary progressive (SP), primary progressive (PP) or progressive relapsing (37).

There have been many studies of MS using MR spectroscopy. Early studies characterized the spectroscopic appearance of demyelinating plaques; it was found that they typically contained high levels of choline (Cho), myo-inositol (mI) and lipids, believed to be due to the accumulation of myelin membrane breakdown products (38), although possibly also due to inflammation (39). At the same time, NAA was decreased suggestive of axonal damage or dysfunction. These changes, particularly low NAA, do not necessarily indicate irreversible axonal damage, however, since, in some patients, restoration of NAA and resolution of the plaques is observed after recovery (40,41). It should be recognized that the spectroscopic appearance of an acute MS plaque may be different from a chronic one; it is generally believed that chronic, “burnt-out” plaques will show a reduction of all metabolites due to its decreased cellularity and increased water content, whereas acute plaques will show elevated Cho (and probably also myo-inositol levels) due to the presence of active demyelination (42).

MRS also offers some insights into the pathology of MS, generally previously only available from post-mortem samples. For instance, even though MRI generally shows discrete lesions in most MS patients, studies using MRSI (43) or whole brain MRS (44) have often found decreased in NAA (and increased Cho) throughout the white matter, both in regions with and without visible abnormalities on conventional T₂-weighted MRI scans, suggesting diffuse brain involvement. This is also confirmed by other MRI techniques sensitive to white matter pathology, such as diffusion tensor (DTI) or magnetization transfer (MT) imaging (45). This suggests that the lesions visible on conventional MRI are perhaps the areas of most severe involvement, but do not necessarily represent well the total disease burden within the brain. It has been found that MRSI measurements of NAA (or the ratio of NAA/Cr) over a large volume of brain tissue appear to correlate better with clinical disability scores, such as the Expanded Disability Status Scale (EDSS), than other measures derived from conventional MRI (46). Although there is some evidence that glial cells may contain NAA, overall, the general belief is that NAA is predominantly located in neurons, axons and dendrites within the mature brain (47). Therefore a correlation of brain NAA levels with EDSS indicates that MRS may provide a measure of axonal loss and/or dysfunction that is a good measure of disease burden in MS. Spectroscopic abnormalities (reduced NAA) may also be found in gray matter (48). These data

also suggest that MRS may have a useful role in evaluating therapeutic response in MS, although to date it has received relatively little attention for this purpose.

It has also been found that reductions in NAA occur early on in the course of MS, which is interesting since the traditional view of MS is that axonal loss occurs secondary to inflammatory demyelination. Therefore, early reductions in NAA support the hypothesis that axonal damage or dysfunction is in fact an early event in the disease process (49).

Even though the spectroscopic features of MS have been very well characterized in the literature, to date there have been relatively few clinical applications of MRS in MS. Probably the most likely area of utility is in *diagnosis*, either early in the stage of the disease (when established diagnostic criteria are not yet fulfilled), or when a patient presents with one or more lesions on brain MRI that are of uncertain etiology.

Early diagnosis can be difficult when patients present with some but not all symptoms characteristic of MS. The diagnosis is made on a combination of clinical findings (2 or more separate episodes of symptoms characteristic of MS), brain MRI, CSF testing for oligoclonal bands, antibodies against myelin proteins, and visual or somatosensory evoked potentials. Patients with isolated optic neuritis, transverse myelitis or internuclear ophthalmoplegia may also eventually be diagnosed with MS. One can certainly hypothesize that an earlier diagnosis of MS would allow earlier therapeutic intervention (e.g. interferon beta-1a) to restrict demyelination or axonal damage that would otherwise occur if therapy was withheld until a 2nd attack of symptoms which would confirm a definitive diagnosis of MS. Since MRS shows spectroscopic abnormalities in white matter with conventional MRI appearance in patients with definitive MS (50), it should therefore also have the potential to identify patients in the earliest stages of demyelination, who may not yet have any MRI abnormalities, or a definite MS diagnosis. In one study, it was shown that 27% of patients with isolated optic neuritis had abnormalities on brain MRS, 25% of whom subsequently developed clinically definite MS within 2 years (51).

The other diagnostic question that may arise is the distinction between lesions of uncertain etiology; for instance, some particularly active, fulminant (tumefactive) MS plaques may be very difficult to distinguish from brain tumors using conventional MRI techniques. Conversely, lesions of other pathological types (e.g. tumors, stroke, infectious diseases) may mimic MS on brain MRI. Tumefactive MS plaques are a problem for MRS, since fulminant demyelination usually produces elevated choline and lactate, and decreased NAA, a pattern very similar to that seen in high grade brain tumors (52). One clue to distinguishing a brain tumor for a patient with tumefactive demyelination may be to evaluate the normal appearing white matter, which in a patient with MS maybe diffusely abnormal, unlike in a patient with a primary, untreated brain tumor, where normal appearing white matter is unlikely to be metabolically abnormal. MR perfusion imaging may also be helpful in distinguishing tumor from demyelination (53).

Acute disseminated encephalomyelitis (ADEM) is a rare, inflammatory demyelinating disease which principally involves brain and spinal cord (54). It affects children and young adults, commonly after an infectious disease or immunization, and often has a similar MRI

appearance to MS. One study has suggested that MRS may be helpful in distinguishing ADEM from MS, based on the observation that ADEM patients with a monophasic disease course and good clinical outcome have normal levels of Cho, unlike the elevation of Cho typically seen in acute MS plaques (41).

Infectious Diseases

The clinical value of MRS in infectious disease has been relatively less well characterized than studies of other CNS pathologies; however, there are some instances where MRS may be helpful in making a diagnosis (55). Since the metabolites observed in MRS reflect the cellular composition of brain, infectious processes of different types that lead to destruction of normal brain tissue tend to exhibit common spectral patterns, such as reduced NAA in neuronal loss, increased Cho and lipids in demyelination and/or gliosis, and reduced levels of all metabolites in necrotic tissue. However, there are some instances where MRS exhibits characteristic patterns, which may be useful for diagnosis.

Intracranial bacterial infections may manifest intra-axially as either cerebritis eventually organizing into an abscess, or meningitis. While MRS has been little used in meningitis, brain abscesses have been well characterized by MRS (55). Normal brain metabolites (Cho, Cr and NAA) are much reduced, and a number of compounds are abnormally elevated, including the cytosolic amino acids valine, leucine and isoleucine (resonating around 0.9 ppm), acetate, lactate, alanine and lipids. In anaerobic bacterial abscesses, the TCA cycle metabolism leads to the elevation of a peak from succinate that can be detected at 2.4 ppm in the spectrum. Succinate elevation has also been observed in cystic lesions resulting from parasitic infections such as cysticercosis or hydatid disease (56,57). Therefore, MRS may provide some clues as to the type of the infective agent, and the metabolic profile of an abscess is quite different from that of a non-infective lesion. For instance, solid, high-grade neoplasia will nearly always have a high Cho signal, although those which are cystic or necrotic may not, in which case spectra from the rim of the lesion (rather than the center) should be reviewed for elevated Cho signal. It should also be noted that the differential diagnosis between an abscess and neoplasm may also be made with diffusion-weighted imaging, which typically (but not always) shows markedly restricted diffusion in the abscess (58).

Viral infections may cause either primary viral encephalitis (i.e. where the virus directly affects the brain) or para- or post-infectious encephalitis where there is no direct evidence of viral penetration into the CNS (e.g. such as ADEM, discussed above). Two of the viral infections most commonly studied by MRS are herpes simplex encephalitis and human immunodeficiency virus (HIV) (59). Both types of encephalitis show reduced NAA and increased Cho and mI, presumably secondary to neuronal loss or dysfunction, and gliosis (60,61). In addition, MRS-based metabolite measures have been shown to correlate with dementia rating scales in HIV, and therefore may be a useful way of quantifying brain involvement in HIV dementia, and as a means of evaluating treatment response (62). Finally, immunocompromised patients with HIV are susceptible to a variety of opportunistic organisms that may flourish in the CNS; the MRI appearance of some of these infectious lesions often overlaps with that of other disease

processes, including neoplasia. For example, the commonly encountered brain mass-like lesions in patients with HIV include toxoplasmosis, progressive multi-focal leukoencephalopathy (PML) and primary CNS lymphoma. These lesions may be difficult to distinguish based on conventional MRI, and it has been reported that MRS may be helpful in establishing the diagnosis (63). In particular, necrotic toxoplasmosis lesions usually show low levels of all metabolites and elevated lipid, while PML and lymphoma will typically have elevated Cho signals. Differentiation of PML from lymphoma may be more difficult, however, based on MRS alone, and other imaging techniques (such as enhancement pattern on post contrast images, or more advanced MR perfusion imaging, or [¹¹C-Methyl]thymidine PET and Thallium-201 SPECT (64)) may be required in order to increase the diagnostic certainty.

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