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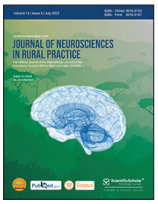

Brief Report

Alkaline pH in intracranial tuberculomas: A ^{31}Phosphorus magnetic resonance spectroscopy study

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ABSTRACT

Objectives: Intracranial tuberculomas are one of the common causes of space-occupying lesions of the brain in developing countries. Proton (^{1}H) magnetic resonance spectroscopy (MRS) has shown lipid peak in intracranial tuberculomas as a characteristic feature. Phosphorus (^{31}P) MRS has been used to evaluate intracranial lesions and to calculate tissue pH non-invasively. The aim of this study is to evaluate intracranial tuberculomas using ^{31}P MRS.

Materials and Methods: Intracranial tuberculomas proven by stereotactic or surgical biopsy were included in the study. After routine T1- and T2-weighted sequences, ^{31}P MRS was performed using single-voxel intravoxel *in vivo* spectroscopy (ISIS) technique in the central core of the tuberculoma (voxel size 1–2 mm^3). The pH was estimated using Petroff's method using the chemical shift between phosphocreatine and Pi.

Results: ^{31}P MRS was available for 26 patients, in which there was significant positive correlation between high-energy phosphate metabolites, (markers of bioenergetic status), and low-energy phosphate metabolites (membrane phospholipids and inorganic phosphate). The calculated pH was slightly alkaline and varied from 6.97 to 7.22.

Conclusion: Intracranial tuberculomas showed alkaline pH in ^{31}P MRS and this may be useful in the characterization of these lesions and possibly also in their treatment.

Keywords: Intracranial tuberculoma, Magnetic resonance spectroscopy, ^{31}P MR spectroscopy, Alkaline pH

INTRODUCTION

Tuberculomas are common form of neurotuberculosis that may present with symptoms of seizures, focal neurological deficits, and/or raised intracranial pressure. Routine CT and MR imaging appearances have been described. In MRI, they appear as isointense in T1-weighted and hypointense in T2-weighted sequences with coalescent nodular or ring enhancement. This is non-specific and may simulate lesions such as other granulomata and neoplastic lesions.[1] There is a need for an objective method of tissue characterization in the diagnostic evaluation of tuberculomas. Proton (^{1}H) and Phosphorus (^{31}P) magnetic resonance spectroscopy (MRS) are based on the biochemical characteristics of the tissue with the advantage of being non-invasive. The previous studies have used proton MRS in the evaluation of tuberculomas by both single- and multi-voxel methods and found that lipid-lactate peak is characteristic of tuberculomas.[2-4] ^{31}P MRS studies of tumors have used to calculate the pH, which is seen to have therapeutic implications. Intracranial tuberculomas are known to have atypical response to treatment. We decided to study the pH of intracranial tuberculomas using ^{31}P MRS which can have potential implications on their treatment.

MATERIALS AND METHODS

Twenty-six patients with intracranial tuberculomas on MRI were included in the study. The diagnosis was based on histopathology, associated pulmonary TB, microbiological features, and response to therapy. The patients were in the age group of 10–50 years and included 16 females and ten males. All the patients underwent MRI on a 1.5 Tesla equipment using quadrature bird cage head coil. The imaging protocol included routine T1-weighted (TR/TE 672/12) and T2-weighted (TR/TE 4800/90) sequences. *In vivo* ^{31}P MRS was also performed on a head quadrature dual-tuned coil in 26 patients. The frequency was tuned for 25.7 MHz for ^{31}Phosphorus. Single-voxel ISIS (Intravoxel *in*

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Received: 12 September 2022 **Accepted:** 30 September 2022 **EPub Ahead of Print:** 02 December 2022 **Published:** 16 December 2022 **DOI:** 10.25259/JNRP-2022-6-25

vivo spectroscopy) technique of TR 400 msec, TE 1 msec, and 512 acquisitions was employed with a total acquisition time of 270 s. Care was taken to include only the central core of the tuberculoma in the voxel [Figure 1]. The voxel size ranged from 1 mm^3 to 2 mm^3. The following peaks were observed (from left to right) – phosphomonoesters (PME), inorganic phosphate (Pi), phosphodiesters (PDEs), phosphocreatine (PCr), and γ, β, and α resonances of adenosine triphosphate (ATP). PCr and total ATP (γ + α + β) represented high-energy phosphates (HEP) and PME, PDE, and Pi constituted low-energy phosphates (LEP). The peak integral values were obtained from the spectrum and the following ratios were calculated: ratios of bioenergetic status (PCr/Pi and β-ATP/Pi) and phospholipid turnover (PME/PDE). The intracellular pH was estimated based on the chemical shift between PCr and Pi.[5] The integral values of metabolites were correlated for significance using Pearson's test ($P = 0.05$).

RESULTS

The individual spectral integral values are summarized in [Table 1]. On Pearson's correlation, significant positive correlation was noted between HEP metabolites (that are markers of bioenergetic status) and LEP metabolites (membrane phospholipids and inorganic phosphate) ([γ, β, α-ATP, PCr, total ATP, and with LEP] [$P = 0.000$, 0.000, 0.034, 0.000, and 0.000, respectively], [Pi, PME, PDE with γ, α-ATP, total ATP, and HEP] [pi 0.022, 0.008, 0.026, 0.038; PDE 0.000, 0.000, 0.000, and 0.000, respectively]). However, there was significant negative correlation between β-ATP/Pi and PME/PDE ratio. The pH was calculated using Petroff's method (Ph = 6.77 + log (δ – 3.23)/(5.70–δ), where δ is the chemical shift observed between the resonances of Pi and PCr) and was found to be alkaline (mean: 7.11, range: 6.97–7.22). A large hump was seen in the spectra ascribed to immobile phosphorus atoms, which is also seen in bone and liver but not in muscle tissue.[6]

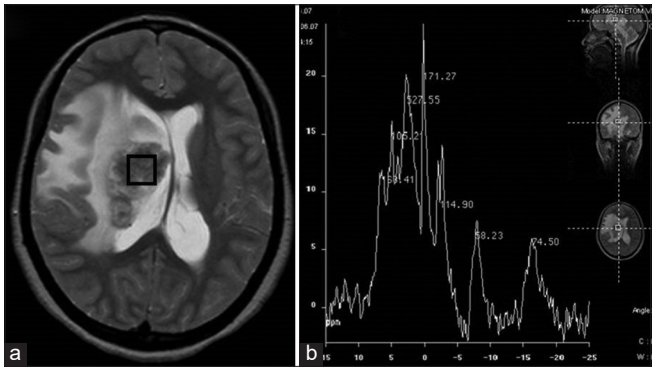

Figure 1: T2 hypointense tuberculoma (a) with ^{31}P-MR spectrum showing the metabolites (b).

DISCUSSION

Tuberculomas constitute one of the common intracranial space-occupying lesions in the developing world. MR has enhanced morphological characterization, but still not specific for a non-invasive diagnosis. The characteristic T2 shortening is due to a combination of factors – caseation, macrophages and their byproducts (free radicals), fibrosis/gliosis, and inflammatory infiltrate. Proton MRS (^{1}H MRS) has been used in the evaluation of intracranial tuberculomas and lipid/lactate peak is considered characteristic, but not pathognomonic of tuberculomas.[2-4,6] In addition, monitoring of therapeutic response of patients to antitubercular therapy is currently based on morphology parameters alone, although *in vivo* proton spectroscopy has also been used.[7] There have been studies of ^{1}H and ^{31}P spectroscopy in various intracranial pathologies such as multiple sclerosis, epilepsy, hypoxic-ischemic injury, dementia, and other degenerative disorders.

In vivo ^{31}PMRS reflects phosphate metabolism in terms of three fundamental processes of the cell – bioenergetics of the cell (indicated by PCr/Pi ratio), cell membrane phospholipid turnover (PME and PDE), and intracellular pH non-invasively. The phosphate metabolites imaged are intracellular, and extracellular concentration of these metabolites is negligible.[8] The major constituents of PME peak are phosphoryl-ethanolamine and phosphorylcholine used in membrane synthesis, whereas the membrane breakdown products – lysophosphatidylcholine, lysophosphatidylethanolamine, glycerophosphorylcholine, and glycerophosphorylethanolamine – contribute to the PDE peak. Choline measured in ^{1}H spectroscopy includes both phosphoryl- and glycerophosphorylcholine apart from other choline containing compounds.[9]

All cellular activities such as membrane transport and protein synthesis require energy supplied in the form of HEP bonds of ATP. In the brain, 40% of the energy released by respiration is required by the membrane ion pump Na^+/K^+ ATPase, even in resting conditions compared to 5% in liver and striated muscle. The sodium gradient maintained by the pump is used as a source for driving other transport mechanisms such as Na^+/Ca^+ exchange and uptake of organic compounds, for example, amino acids. It is also important in maintaining resting membrane potential and for regulation of cell volume. Thus, the increased glucose metabolism resulting from nervous stimulation is largely used for restoring the ionic gradients across the membrane.[10,11]

There was significant positive correlation between high-energy phosphate metabolites that are markers of bioenergetic status and LEP metabolites that consist of membrane phospholipids and inorganic phosphate ([γ, β, α-ATP, Pi, total ATP, and with LEP], [PCr, PME, and PDE with γ, α-ATP, total ATP, and HEP]). However, there was significant negative

Table 1: ^{31}P MRS integral values in 26 patients and calculated pH.

S. No	PME	Pi	PDE	PCr	g-ATP	a-ATP	b-ATP	pH
1	162.1	53.62	563.85	203.33	117.31	90.6	78.58	7.09
2.	138.11	159.81	633.17	168.2	137.45	34.18	29.27	7.09
3.	177.67	105.31	550.71	251.28	140.18	84.38	62	7.17
4	198.77	124.55	680.71	286.79	160.75	105.42	76.56	7.13
5	219.51	131.47	1360.00	469.25	283.44	237.78	126.36	7.13
6	45.46	81.61	734.69	300.37	143.89	82.49	57.86	7.09
7	163.41	105.21	527.85	171.27	114.9	58.23	74.5	7.04
8	213.86	102.03	717.69	231.19	162.62	117.93	91.27	7.09
9	147.18	89.08	475.48	221.78	134.73	88.72	75.4	7.09
10	138.11	133.44	452.97	364.68	171.85	140.42	67.74	7.22
11	30.91	72.14	696.29	200.04	135.96	33.47	178.41	7.13
12	100.31	98.84	368.4	325.12	134.78	92.59	53.59	7.04
13	208.22	118.52	787.69	260.86	172.67	119.8	86.98	7.09
14	181.51	143.57	658.45	180.64	136.81	84.25	87.44	6.97
15	113.95	112.63	801.25	362.42	175.76	121.27	89.18	7.13
16	247.14	109.27	666.53	310.97	147.91	116.67	87.39	7.17
17	130.67	109.84	538.21	270.29	151.93	117.46	64.16	7.13
18	143.94	79.42	599.24	245.41	145.44	106.92	77.74	7.13
19	168.28	91.23	524.23	114.11	117.28	77.05	81.31	7.08
20	139.85	41.33	424.92	119.05	82.44	66.24	77.76	7.04
21	120.15	77.14	453.83	164.17	105.41	59.33	45.4	7.08
22	201.3	49.91	474.43	338.83	36.87	121.21	71.56	7.21
23	171.61	89.37	541.15	173.49	123.51	84.51	73.79	7.08
24	106.78	72.44	347.65	203.9	103.2	89.69	47.74	7.17
25	224.74	81.38	577.12	183.49	144.32	87.83	81.36	7.08
26	91.54	57.24	403.76	130.43	93.23	67.58	67.4	7.08

PME: Phosphomonoesters, Pi: Inorganic phosphate, PDE: Phosphodiesters, PCr: Phosphocreatine, ATP: Adenosine triphosphate

correlation between β-ATP/Pi and PME/PDE ratio ($P = 0.045$) suggesting that although the changes in phosphate pool are synchronous within a cell, the processes of bioenergetic state and membrane phospholipid turnover may not be parallel. Similar changes with varied correlations have been reported in intracranial tumors without consistency and may probably reflect underlying biophysical processes that vary among individuals perhaps enhancing our understanding of such subcellular processes, but may not be discriminating enough to differentiate between tuberculomas or tumors and other similar lesions in their diagnosis.[12-15]

The pH in the core of the tuberculomas found using the Petroff's method (from chemical shifts of PCr and Pi) was alkaline and varied between 6.97 and 7.22. This paradoxical alkalosis may be due to many reasons. First, glial and phagocytic cells have higher intracellular pH; second, altered cell-buffering mechanisms like Na^+/H^+ antiporter; third, creatine phosphokinase reaction producing ATP consuming H^+ (CPK and PCr are present in glial cells also); and finally, metabolic paralysis, cell death, and intracellular edema resulting in equilibration of intra- and extracellular bicarbonate ions.[16,17] Experimental study done using acetazolamide in healthy volunteers did not produce any significant changes in the pH of normal brain tissue measured using ^{31}P MRS, though extracellular pH dropped. This lack of change in pH (which is mainly intracellular) has been ascribed to similar buffering mechanisms.[18]

Both acidosis and alkalosis have adverse effects on cellular function. Acidosis has major deleterious effects on mitochondrial respiratory function and post-ischemic mitochondrial function. In experimental ischemic models, alkalosis is associated with partial or complete loss of ATP, and regions of alkalosis had lowered oxygen extraction fraction with subsequent reperfusion. In fact, severe tissue alkalosis is considered as "physicochemical marker" of advanced tissue injury.[17]

CONCLUSION

This alkaline pH may have therapeutic implications as some tuberculomas are known to be resistant to routine antituberculous agents or show delayed response requiring up to 24 months of antituberculous therapy. The finding of alkaline pH explores the possibility of suitable agents of appropriate pH to reach the core of the lesions for early treatment response.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Jayakumar PN, Nagarajan K. Alkaline pH in intracranial tuberculomas: A ^{31}Phosphorus magnetic resonance spectroscopy study. J Neurosci Rural Pract 2022;13:791-4.