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Mr Textural Features (Radiomics) For Predicting Response to Treatment in Patients with Intracranial Tuberculoma: A Retrospective Cross-Sectional Study

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MR TEXTURAL FEATURES (RADIOMICS) FOR PREDICTING RESPONSE TO TREATMENT IN PATIENTS WITH INTRACRANIAL TUBERCULOMA: A RETROSPECTIVE CROSS-SECTIONAL STUDY

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ABBREVIATIONS

CNS = Central Nervous System

TB = Tuberculosis

CT = Computed Tomography

PET = positron emission tomography.

MRI = Magnetic Resonance Imaging

GLCM = Grey level co-occurrence matrix

NGLDM = Neighborhood grey level different matrix

GLRLM = Grey level run-length matrix

GLZLM = Grey level zone length matrix

GLRLM SRE = Grey level run-length matrix short run emphasis.

GLRLM LRE = Grey level run-length matrix long run emphasis.

GLRLM HGRE = Grey level run-length matrix high grey level run emphasis.

GLRLM SRLGE = Grey level run-length matrix short run low grey level emphasis.

GLRLM SRHGE = Grey level run-length matrix short run high grey level emphasis.

GLRLM LRLGE = Grey level run-length matrix low run low grey level emphasis.

GLRLM LRHGE = Grey level run-length matrix low run high grey level emphasis.

GLRLM GLNU = Grey level run-length matrix grey level non uniformity.

GLRLM RLNU = Grey level run-length matrix run length non uniformity.

GLRLM RP = Grey level run-length matrix run percentage.

NGLDM = Neighborhood grey level different matrix

GLZLM = Grey level zone length matrix

GLZLM SZE = Grey level zone length matrix short zone emphasis

GLZLM LZE = Grey level zone length matrix long zone emphasis

GLZLM LGZE = Grey level zone length matrix low grey zone emphasis

GLZLM HGZE = Grey level zone length matrix high grey zone emphasis

GLZLM SZLGE = Grey level zone length matrix short zone low grey level emphasis

GLZLM LZLGE = Grey level zone length matrix long zone low grey level emphasis

GLZLM GLNU = Grey level zone length matrix grey level non uniformity.

GLZLM ZLNU = Grey level zone length matrix zone length non uniformity.

GLZLM ZP = Grey level zone length matrix zone percentage.

GLZLM SZHGE = Grey level zone length matrix short zone high grey level emphasis.

ABSTRACT

Background and objective:

MR based radiomics can potentially response to treatment in intracranial tuberculoma, but very scarce literature is available in this regard. The purpose of this study was to determine whether MR based radiomic features can be used to predict response to antituberculosis (AT) treatment.

Methods:

Data of patients with intracranial tuberculomas who underwent MR imaging and AT treatment at our institution during the last 10 years was analyzed. In each case follow-up imaging performed at 6 months post initiation of treatment was reviewed to establish response to treatment. The textural analysis was performed by two consultant neuroradiologists, using open-source software (Lifex) with FLAIR coronal image after contrast administration from pretreatment MRI study radiomic analysis.

Results:

Twenty-four patients with mean age 33.8 years were included in the study. Sixteen patients were in the treatment responsive group while eight patients were in the treatment resistant group. Thirty-eight radiomic parameters were extracted for each patient. There was a significant difference in three out of 38 parameters (histogram skewness, GLCM correlation and NGLDM Coarseness) in patients amongst the two groups. Logistic regression model was developed using these parameters which accurately predicted 83.3% of the cases according to the response to the AT treatment ($\chi^2=11.517$, $p=0.003$). ROC curve analysis was performed using histogram skewness which showed acceptable discrimination ($p=0.037$ and 95% CI =0.577-0.954) for predicting the response to treatment.

Conclusion:

MR textural parameters (histogram skewness, GLCM correlation and NGLDM Coarseness) may be used as imaging biomarkers to predict response to treatment in patients with intracranial tuberculoma.

Key Words: Intracranial tuberculoma, CNS tuberculosis, Radiomics, Textural analysis, treatment

INTRODUCTION

Intracranial tuberculoma are one of the commonest manifestations of central nervous system (CNS) tuberculosis (TB).¹ They are described as evolving granulomas in the brain, formed because of nervous systems immune response to the invasion of TB pathogen. These lesions are known to have various signals on conventional MRI imaging depending upon its stage of evolution.^{2,3} MRI spectroscopy has proven to be a useful modality at differentiating these lesions from other intracranial pathologies including infections and malignancy.⁴ Published literature describes the effectiveness of CT perfusion markers in differentiating treated and untreated tuberculomas, however to the best of our knowledge no clinical and imaging method exists which can predict the response to treatment in a brain tuberculoma at initial presentation.⁵ Prediction of treatment response can help streamline treatment plan, allow early counseling of the patient, and help in prognostication.⁶

Radiomics is a translation field which aims at extracting quantifiable data from medical images using software.⁷ The role of MR based radiomic features is getting established in various intracranial pathologies including tumors and neurodegenerative disorders.⁸⁻¹³ CT and PET CT based radiomic models have been developed which can help differentiate pulmonary tuberculosis from lung cancer, however no literature exists which describes the role of MR based radiomic features in intracranial tuberculoma.^{14,15} The aim of our study was to assess whether MR based radiomic features can be used to predict response to treatment in intracranial tuberculoma.

METHODS

Study design: Retrospective cross-sectional study.

Place and duration of study: This study was conducted in the department of neurology and radiology, of Aga Khan University Hospital, Karachi.

Sample size: OpenEpi was used to calculate sample size. Considering global prevalence of CNS tuberculosis to be 1% amongst all Tuberculosis patients, a minimum sample size of 15 was considered to be adequate for this study. This study included 24 patients.

Sampling technique: Non-probability consecutive sampling.

Data collection: Patients aged 18 years and above of either gender, who were treated for intracranial tuberculomas and underwent pre and post treatment MRI brain examination with contrast were included. Our departmental radiology repository search engine was used to collect data retrospectively with key words “intracranial tuberculoma” and “MRI”. Figure 1 explains the methodology of our patient selection. One-hundred-eighty-one cases appeared with our keywords, who underwent MRI brain with and without

contrast with clinical suspicion for intracranial tuberculoma in a period of 10 years (from July 2009 – June 2019). Sixty-four patients were excluded based on non-availability or non-diagnostic clinical data for intracranial tuberculoma as per our inclusion criteria. Forty-seven patients were excluded as MRI was negative for intracranial tuberculoma. Another 16 patients were excluded based on history of prior surgery, coexisting demyelinating disorder, infection, or tumor. While further 34 patients were excluded due to non-availability of follow up MRI examination. The final cohort included 24 patients who were diagnosed with intracranial tuberculomas based on our criteria explained in section case ascertainment, administered standard anti tuberculous treatment at our neurology outpatient clinic and underwent MRI brain with and without contrast before and after initiation of treatment at an interval of six months.

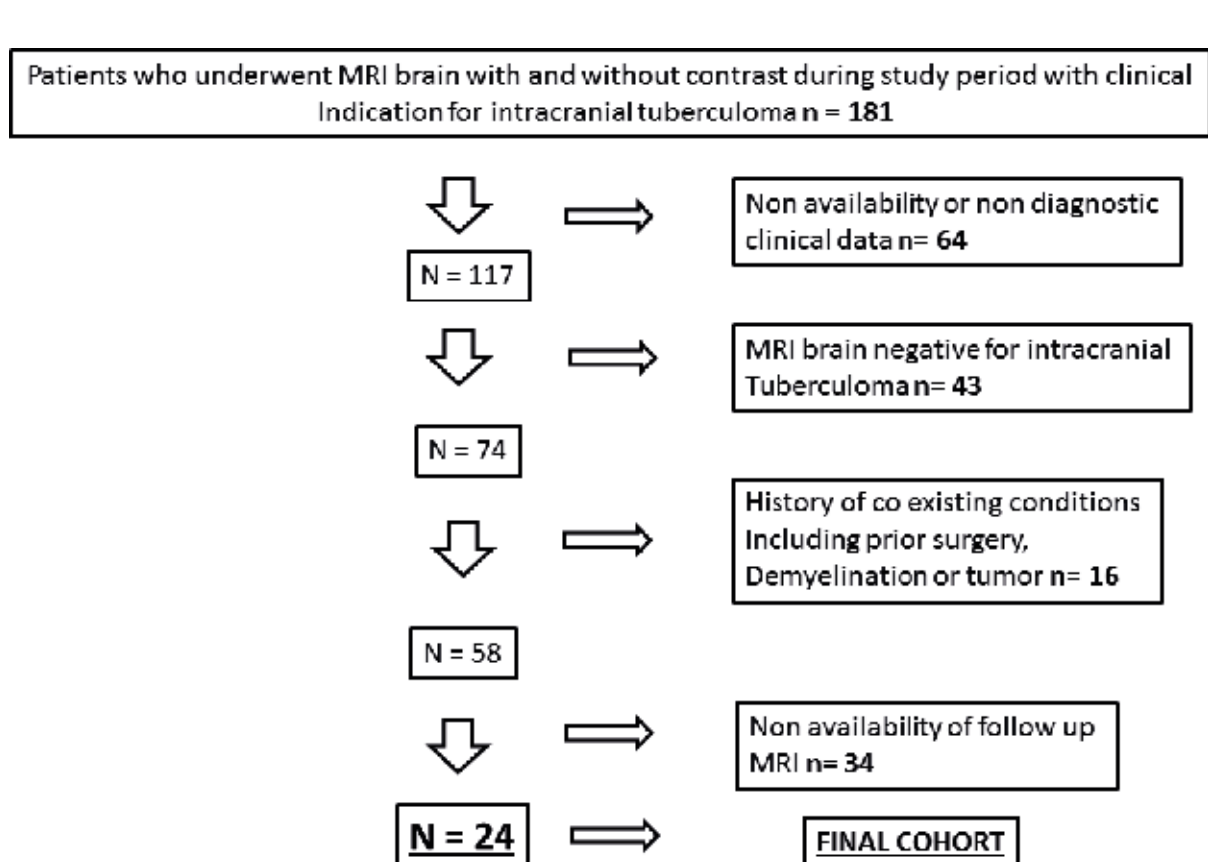


Figure 1: Methodology of patient selection

Case ascertainment: All 24 patients had a space occupying intracranial lesions on MRI brain with contrast examination. The most characteristic feature uniform to all lesions was peripheral ring enhancement on T1 and FLAIR post contrast images. The diagnosis was confirmed by presence of one of the following clinical and laboratory features in addition to the MRI finding suggestive of central nervous system tuberculosis including histopathology (3 patients); cerebrospinal fluid culture (9 patients); Genexpert (3 patients), response to treatment (3 patients) and multiple aforementioned criterias positive for tuberculous etiology (6 patients). All patients received four-drug anti tuberculous therapy (Rifampicin, Isoniazid, Pyrazinamide and Ethambutol) for three months and then three drugs (excluding ethambutol) for further 9-12 months. All patients received oral steroids for 4-6 weeks in tapering doses.

Imaging follow up and determination of response to treatment: 11/24 patients underwent a single follow up MRI study post initiation of treatment, while 13/24 patients underwent 2-4 follow up studies. The six months post initiation of treatment MRI examination was considered to evaluate the radiological response to treatment based on previous reports.¹⁶ A patient was labeled treatment responsive based on one of the following MR features 1) interval

reduction in the number of tuberculomas 2) Interval resolution of all intracranial tuberculomas, 3) Interval reduction in size of tuberculomas, 4) Interval reduction or resolution of perilesional edema. A patient was labeled as treatment resistant based on one of the following MR imaging features including 1) interval increase in size of preexisting intracranial tuberculomas 2) Interval progression in number of intracranial tuberculoma 3) Interval no change in size and number of intracranial tuberculomas. The occurrence of associated events including development/resolution of infarction, hydrocephalus or meningeal enhancement were recorded but were not used for establishing response to AT treatment in this study.

MRI scan in each patient before and after treatment was performed on a 1.5 T siemens MAGNETOM Avanto MR image scanner. Each scan was a multiplanar and multi sequential scan performed with and without contrast. The image acquisition parameters were according to standard departmental protocol for intracranial lesions (Table 1). The sequences included in each scan were T1-weighted axial pre and post contrast, T2-weighted axial, T2-weighted sagittal, FLAIR pre and post contrast Coronal images, DWI/ADC weighted axial, SWI axial and T1-weighted post contrast sagittal images.

Table:1 Scan parameters and sequences included in standard departmental protocol of MRI brain with and without contrast for evaluation of intracranial lesions.

Scan parameters	T1	T2	FLAIR	DWI	ADC	SWI	T1 post contrast	FLAIR post contrast
Plane	Axial	Axial / sagittal	Coronal	Axial	Axial	Axial	Axial / sagittal	Coronal
Direction	Row	Row / Row	Row	COL	COL	Row	Row / Row	Row
REP Time (ms)	500	4430 / 6530	9000	3600	3600	49	500 / 500	9000
Echo time (ms)	7.8	97 / 106	109	115	115	40	7.8 / 7.8	109
Echo train (ms)	1	13 / 25	21	96	96	1	1 / 1	21
Echo number	1	1 / 1	1	1	1	1	1 / 1	1
Slice thickness (mm)	5	5 / 5	5	5	5	2	5 / 5	5
Slice spacing (mm)	6.5	6.5 / 6.5	6.5	6.5	6.5	0	6.5 / 6.5	6.5
Acquisition type	2D	2D / 2D	2D	2D	2D	3D	2D / 2D	2D

Conventional MR Imaging Analysis: The Digital Imaging and Communications in Medicine (DICOM) images of the MRI brain were retrieved from the picture archiving and communication system (PACS) and were anonymized. Two consultant neuroradiologists with more than five years post national board certification reviewed all the MRI scans. At the time of interpretation, they were blinded to the patient's clinical

data including the outcome of disease. The purpose of reviewing conventional imaging was to select the largest and most well defined intracranial tuberculoma on a FLAIR post contrast coronal image for the purpose of radiomic analysis. Associated features of intracranial tuberculoma including meningeal enhancement, hydrocephalus and infarctions were recorded on a structured Performa.

MR textural analysis (Radiomic):

MR texture analysis was performed using freely available open-source software (LIFEx version 4.70, LifexSoft, Orsay, France).¹⁷ The two consultant radiologists extracted the local image features according to the standard software documentation. Both radiologists were blinded to the clinical and outcome data of the patient. FLAIR coronal image after contrast administration from pretreatment MRI study was used for radiomic analysis. This image and sequence were chosen as most of the tuberculoma were visualized in full profile on a coronal image, therefore it was easier to define a region of interest on

a tuberculoma lesion on this image. Region of Interest (RoI) was carefully drawn on the intracranial tuberculoma on the slice making sure not to include any structure or tissue outside the tuberculoma as shown in Figure 2. The software then automatically calculated a total of 38 textural parameters. These included 6 histogram-based parameters, 7 Grey level co-occurrence matrix (GLCM) based, 3 Neighborhood grey level different matrix (NGLDM) based, 11 Grey level run-length matrix (GLRLM) and 11 Grey level zone length matrix (GLZLM) related features. All 38 textural parameters are mentioned in Table 2.

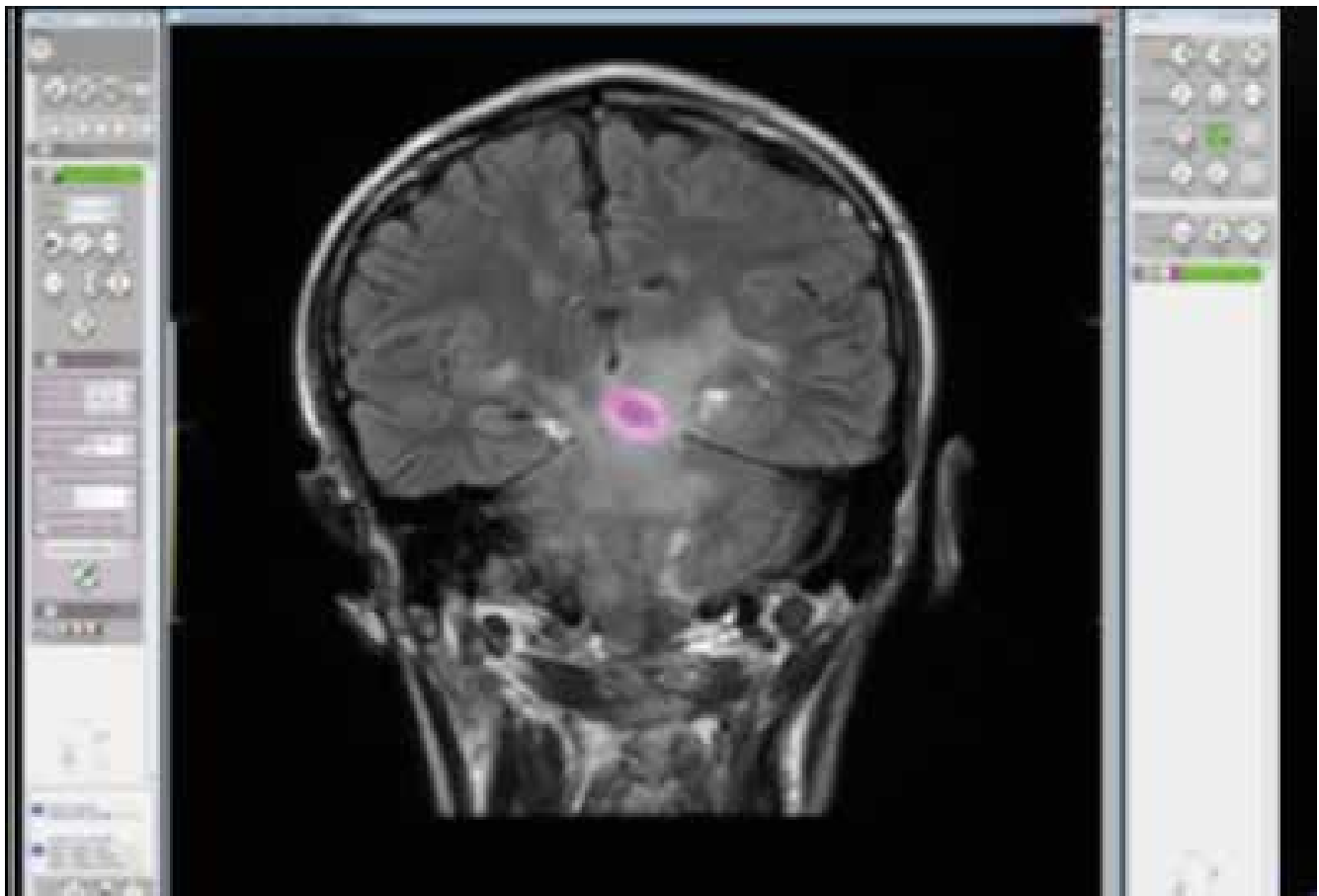


Figure 2: Coronal post contrast image with region of Interest (ROI) represented by a pink circle, drawn on the tuberculoma with image opened in the life X Software undergoing textural analysis extraction.

Table 2: 38 textural parameters extracted using life x open-source software.

S.no	Histogram based	GLCM based	GLRLM based	NGLDM based	GLZLM based
1	Histogram Skewness	GLCM Homogeneity	GLRLM SRE	NGLDM Coarseness	GLZLM SZE
2	Histogram Kurtosis	GLCM Energy	GLRLM LRE	NGLDM Contrast	GLZLM LZE
3	Histogram Excess Kurtosis	GLCM Contrast	GLRLM LGRE	NGLDM Busyness	GLZLM LGZE
4	Histogram Entropy Log 10	GLCM Correlation	GLRLM HGRE		GLZLM HGZE
5	Histogram Entropy log 2	GLCM Entropy log 2	GLRLM SRLGE		GLZLM SZLGE

Statistical analysis:

SPSS version 20 was used for statistical analysis. Qualitative variables were expressed as frequency (percentage). Quantitative variables were expressed as mean $\pm$ SD. An independent Sample's t-test was used to compare various MR textural parameters in patients who responded versus those who did not. Logistic regression and ROC curve analysis was performed to develop a model for predicting the response to treatment based on significant MR Radiomic features. A p-value of less than .05 was considered statistically significant.

Ethics:

An exemption was obtained from the institutional ethical review committee for this study and requirement for informed consent was waived off.

RESULTS

Our study cohort consisted of 10 men and 14 women, aged 13-79 years (mean 33.8 years). Most common clinical presentation in this cohort was headache along with fever (six cases), fever with new onset focal

neurologic deficit (five cases) and drowsiness (four cases). Seven patients were referred for imaging with a labeled diagnosis of CNS tuberculosis, for evaluation of disease extent while three patients presented with seizures.

Our cohort comprised of 16 patients in treatment responsive group and eight patients in treatment resistant group. During review of follow up clinical notes at 3-6 months interval, amongst the treatment responsive group no new onset headache, seizure or drowsiness was documented, while in the treatment resistant group 1/8 patient reported new onset seizure, 1/8 patients complained of new onset headache. Remaining six patients reported no new onset neurological symptom. Comparison of associated features and complications of intracranial tuberculomas was observed and compared between the treatment responsive and treatment resistant group on conventional MRI brain with contrast examination. 4/16 patients (25%) from the treatment responsive group had a solitary intracranial tuberculoma, however all other patients from both groups had multiple

lesions. Hydrocephalus was present in 7/16 (43%) patients in the treatment responsive group, and it was documented in 4/8 (50%) in resistant cases. Territorial infarctions were documented in equal proportion in both groups. 2/16 (12.5%) cases in the responsive group and 1/8 (12.5%) patients in the resistant group had coexistent intra and extra axial tuberculomas, however all other patients in both groups had intra axial

lesions. Meningeal enhancement was documented in 7/16 (43.7 %) cases from the responsive group, and it was seen in five of eight cases (62%) in the resistant group. No statistically significant difference was found in the conventional MRI features in the responsive and resistant cases (Table 3). Example of a treatment responsive case is described in Figure 3 (a-g) and a treatment resistant case is described in Figure 4 (a-d).

Table 3: Comparison of conventional MRI findings in treatment responsive and resistant group.

Parameter	Responsive group (n = 16)	Resistant group (n=8)
Hydrocephalus	7	4
Infarctions	2	1
Intraaxial tuberculomas	14	7
Coexistent Intra and extra axial lesions	2	1
Solitary versus multiple	4+12	8 (Multiple)
Meningeal enhancement	7	5

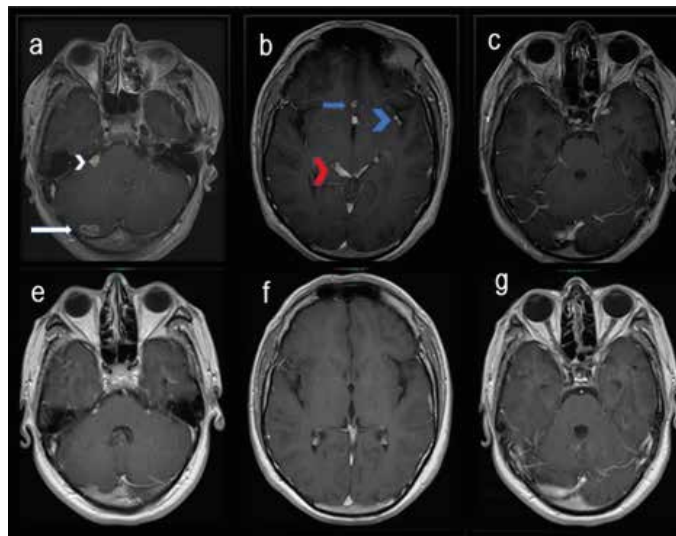


Figure 3: Pretreatment (a-c) contrast enhanced axial sections through brain reveal irregular shaped peripherally enhancing lesions in right cerebellar hemisphere posteriorly (white arrow), right cerebellopontine angle (white arrowhead), interhemispheric cistern (blue arrow), left sylvian cistern (blue arrowhead) and peri mesenteric basal cistern (red arrowhead). Subsequent follow up contrast enhanced MRI brain axial images (e-g) reveal interval resolution of above-described lesions representing response to treatment.

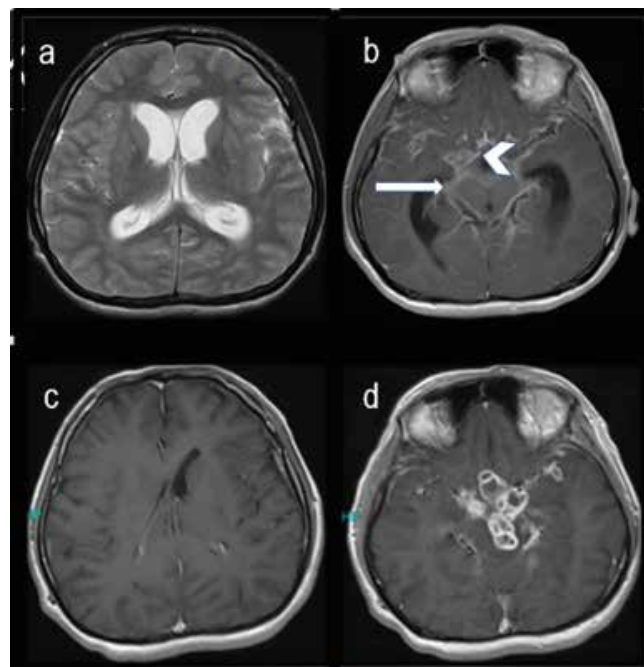


Figure 4: (a, b) pretreatment MRI brain examination off a 13-year-old boy, diagnosed case of central nervous system tuberculosis through GeneXpert following CSF sampling, axial T2 weighted image and post contrast T1 weighted image shows hydrocephalus, thick basal meningeal enhancement (white arrow) and a peripherally enhancing lesion (white arrowhead) in basal cistern. Post treatment MRI brain examination (c, d) shows interval resolution of hydrocephalus secondary to placement of shunt, however there is interval increase in the number of peripherally enhancing lesions representing paradoxical response / resistance to standard medical treatment.

A total of 38 MR textural features were extracted. Statistically significant difference (p value of less than 0.05) was observed in values of 3/38 textural parameters between treatment responsive and resistant groups: Histogram skewness , GLCM correlation and NGLDM Coarseness, respectively. The difference in values of these parameters in the two groups and their p value is detailed in Table 4. Logistic

regression analysis was performed using these three parameters which correctly classified 83.3% of cases as treatment responders versus non-responders. ($\chi^2=11.517$, $p=0.003$). ROC curve analysis using histogram skewness showed acceptable discrimination ($p=0.037$ and 95% CI =0.577-0.954) for predicting the response to treatment.

Table 4: Textural parameters with statistically significant difference in values amongst treatment responsive and treatment resistant cases.

Textural Parameter	Value in responsive cases	Value in resistant cases	p-Value
Histogram Skewness	.1350562500000000	.3020000000000000	0.040
GLCM correlation	.6037500000000000	.4472500000000000	0.038
NGLDM Coarseness	.0349937500000000	.0167625000000000	0.032

DISCUSSION

Tuberculoma in the brain can be differentiated on various grounds. One such parameter is location of the tuberculoma which can be intra-axial and extra-axial / meningeal based lesions.^{18,19} Another parameter is the signal of the tuberculoma lesion on conventional MRI imaging based on which a tuberculoma can be classified as non-caseating, caseating granuloma with liquefied center and caseating granuloma with solid center.²⁰ Tuberculomas can also be differentiated into treated versus untreated types, however the most important differentiation which impacts the patient management and treatment strategy is the response of the tuberculoma to the standard anti tuberculous treatment.^{5,16} A typical intracranial tuberculoma is thought to arise secondary to enlargement of a tubercle without rupture into subarachnoid space, however enlargement of a tuberculoma in brain during treatment occurs as a result of delayed hypersensitivity response of the host immune system to the destructed mycobacterial products secondary to the anti-tuberculous drug treatment.²¹ This eventually results in the radiologically progression in the disease process with or without clinical deterioration.²²

Recent advances in conventional imaging including sequences such as perfusion weighted imaging, diffusion weighted imaging and MR spectroscopy have significantly improved the diagnosis of intracranial tuberculomas and its differentiation from closely mimicking pathologies, however to the best of our knowledge no clinical or imaging method exists, which at source can determine the treatment response in intracranial tuberculomas.^{23,24} In our cohort also we observed that conventional MRI imaging cannot reliably differentiate the two types of responses. Therefore, development of an image-based tool which at source can predict the eventual outcome of disease and separate responsive versus resistant cases can be extremely helpful, which can allow making a wise choice between various medical and surgical treatment options, determination of the treatment outcome and early counseling of patient regarding approximate expectation.

Radiomics is an evolving field which involves extracting quantitative information from clinical images to improve diagnostic accuracy.⁷ Several sets of radiomic features exist, however adherence to standardized set of radiomic features is important to enable verification

and validation of the information extracted.²⁵ Three radiomic features include histogram skewness, GLCM correlation and NGLDM Coarseness showed statistically significant difference in treatment responsive and resistant group. Histogram based textural features are first order features which are based on the level of grey within an image. Histogram skewness is a more sophisticated feature which describes the asymmetry of the intensity distribution curve.²⁶ Grey level co-occurrence matrix (GLCM) correlation is a second order textural feature which is a biomarker for heterogeneity of spatial and intensity information within a lesion. It has already proven its worth as a biomarker in work up of tumors.²⁷ The last parameter showing statistically significant difference in our results is neighborhood grey level dependence matrix (NGLDM) coarseness. This feature utilizes the average of neighborhood pixels to determine variation in texture.²⁷

In our study 3/38 radiomic parameters including Histogram skewness, GLCM correlation and NGLDM Coarseness depict statistically significant difference in

values amongst treatment responsive tuberculomas and tuberculomas which show progression or no change despite treatment. Based on available literature the findings of our study indicate that treatment responsive and resistant tuberculomas demonstrate difference in intensity distribution curve, internal difference in spatial and intensity information and have difference in average of grey levels within its pixel and henceforth possess variation in their texture.

Limitations of this study include small sample size, lack of long-term imaging follow up, retrospective method of data collection and a single sequence that is post contrast FLAIR coronal image analysis. Future studies comparing multiple software and images of different sequences can help in further analyses of the role of radiomics in the domain of intracranial tuberculomas.

CONCLUSION

MR textural parameters (histogram skewness, GLCM correlation and NGLDM Coarseness) may be used as imaging biomarkers to predict response to treatment in patients with intracranial tuberculoma.

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Authors' contribution:

Muhammad Awais; concept, data collection, data analysis, manuscript writing, manuscript review

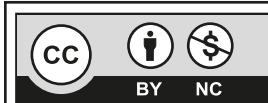
Shahmeer Khan; concept, data collection, data analysis, manuscript writing, manuscript review

Mohammad Wasay; concept, data analysis, manuscript writing, manuscript review

Muhammad Azeemuddin; data analysis, manuscript writing, manuscript review

Ayesha Shoukat; data collection, data analysis, manuscript writing, manuscript review

Hafsa Khan; data collection, data analysis, manuscript writing, manuscript review



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