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Original Article

Radiology Section

Role of Diffusion Weighted Imaging and MR Spectroscopy in Characterisation of Intracranial Neoplasms

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ABSTRACT

Introduction: MR Imaging plays an important role in the evaluation of intracranial tumours. Conventional MRI, despite its excellent soft tissue characterization, fails to provide details about grading and infiltration of tumours. Advanced MR sequences like diffusion weighted (DW) and MR spectroscopy (MRS) can differentiate between low grade and high grade tumours and thus help the clinician in management of brain tumours.

Objective: To localize and characterise various intracranial masses on conventional MR sequences, to assess the usefulness of DW and MRS in characterising the mass lesions and to correlate the inferences with histopathology or clinical follow up.

Materials and Methods: Total of 67 patients over a period of one year, presenting to the department of Radiodiagnosis and Imaging, Dayanand Medical College and Hospital, Ludhiana, were included in this study. Conventional MR sequences along with DW and MRS were done after taking localisers in all the three planes.

Results: Most common cerebral neoplasms were metastases followed by Glioblastoma Multiforme (GBM). Male: female ratio was 1.5:1. Headache was the most common presenting complaint. Apparent Diffusion Coefficient (ADC) values were similar in GBM and metastases but were higher in low grade gliomas. On MRS, choline levels in the areas of diffusion restriction were higher and NAA levels were lower in cases of GBM, metastases and lymphoma as compared to low grade gliomas.

Conclusion: DW imaging with ADC values and MRS in combination with conventional MRI are very useful in detection of brain tumours and distinguishing low grade from high grade tumours.

Keywords: Apparent diffusion coefficient, Choline, Gliomas, Metastases, N- Acetyl aspartate

INTRODUCTION

MR Imaging plays an integral role in the evaluation of intracranial tumours. It is the most important non-invasive tool for detection, pre surgical planning and assessing the response of cerebral tumours to treatment. Although conventional MRI has excellent soft tissue characterisation and a number of imaging sequences, it fails to provide details about grading and infiltration of tumours [1].

Advanced MR techniques in addition to conventional sequences have added to its role in providing details of physiological data and metabolic activities in brain tumours [2]. MR spectroscopy and diffusion imaging allow us to predict the chemical nature of compounds, haemodynamic characteristics, microvascular integrity and the free movement of water molecules within the mass lesions [3]. This has significantly changed the treatment scenario. Nowadays, MR sequences like DW and MRS can differentiate between low grade and high grade tumours and thus help the clinician in planning treatment and determining the prognosis. Most of the studies in literature describe the role of single sequence in tumour grading. We in the present study describe the role of integrated approach by using DW imaging and MRS in addition to conventional sequences in delineating the extent and grading intracranial tumours and finally correlated with histopathology or clinical follow up.

AIMS AND OBJECTIVES

1. To study the conventional MRI features of cerebral tumours.

2. To study the role of diffusion weighted imaging (DWI) and MR Spectroscopy (MRS) in differentiating low grade tumours from high grade tumours.

3. To correlate the inferences with final histopathology diagnosis or clinical follow up.

MATERIAL AND METHODS

Source of Data

Clinically diagnosed/ suspected cases of intracranial tumours referred to the department of Radiodiagnosis and Imaging in

Dayanand Medical College and Hospital, Ludhiana, for MRI evaluation over a period of 12 months duration from January 2015 to January 2016, were subjected to comprehensive MR imaging evaluation.

Methods of Collection of Data

This was a longitudinal, prospective study. Patients were subjected to a multiplanar, multisequential MRI scan of the brain on a MAGNETOM AVANTO 18 Channel 1.5 Tesla TIM MR Machine by Siemens India Ltd. in the department of Radio diagnosis and Imaging. The institutional ethical committee accorded ethical clearance to this study. Informed consent and detailed clinical history was taken from each patient. The confirmation of the diagnosis was done histopathologically or on follow-up scans.

Inclusion Criterion

All clinically diagnosed/suspected patients with intracranial tumours were included.

Exclusion Criterion

All cases without any intracranial mass on MRI and having claustrophobia, metallic implants, cardiac pacemakers and metallic foreign body were excluded. Patients with infective aetiology were excluded while interpreting the data.

Preparation of patient

All metallic objects and articles such as jewelry, credit cards, watches, keys, coins etc. were taken from the patient and kept in a locker before examination. Expected time of scan and the procedure was also explained to all the patients in their vernacular language. During the scan, patients were in contact with the technician/doctor by a two-way intercom system.

MR Protocol

After proper positioning of patients, localisers were taken in coronal, sagittal and axial planes. The MRI protocol consisted of the following sequences:

In the axial plane: Turbo spin echo (TSE) T2W sequence [repetition time(TR)/echo time(TE)/number of excitations (n)=4050ms/101ms/3] ,Spin echo (SE) T1W sequence (TR/TE/n=652ms17ms/1),FLAIR-Fluid attenuated inversion recovery sequence (TR/TE/n=9000ms/1; inversion time, 2500ms), GRE sequence (TR/TE= 761ms/26ms), FLAIR sequence in coronal plane and T2W sequence in sagittal plane, Contrast enhanced T1W sequence,diffusion weighted (DW) imaging using echo planar imaging (EPI) sequence with TR/TE =3500ms/109ms (minimum), field of view = 23cmX 23cm,number of excitations =3, slice thickness=5mm, inter-slice gap = 1.5mm, matrix size =128X128. Diffusion sensitizing gradients were applied along the three orthogonal directions with diffusion sensitivity of b=0, b=500 and b= 1000s/mm2.

Image guided multi voxel proton MR spectroscopy was performed using stimulated echo acquisition mode (STEAM) technique. STEAM sequence parameters used were (TR/TE/n= 1500/270/4) and (TR/TE/n= 1500/135/4) each with acquisition time of 7.12 minutes. The size and position of voxel were carefully selected so as to place it well within the lesion and the spectra were not affected by surrounding healthy tissue.

Parameters studied: Metabolite concentrations of N-acetylaspartate (NAA), choline, lipid, lactate and creatine were measured in the lesion area and a similar area in the contralateral side, which were used as a control. Ratio of the peak areas i.e. NAA/ Choline, NAA/Cr and choline/creatine were determined from each spectrum. Spectra from different categories of patients were compared with each other.

STATISTICAL ANALYSIS

The data was recorded in a proforma and was analysed using descriptive statistics. Various numerical tools like mean, standard deviation and p-value and graphical tools like histogram and pie chart were used to analyse the data.

		Age group (years)							
		0-10	11-20	21-30	31-40	41-50	51-60	61-70	>70
Metastases		-	-	-	-	9	7	7	2
High gd. Gliomas	GBM	-	-	-	1	4	10	4	2
	AO	-	-	-	-	-	-	1	-
Low gd. Gliomas	ODG	-	-	-	-	1	-	-	-
	OA	-	-	-	1	-	-	-	-
	DA	-	-	-	1	-	-	-	1
	BG	1	2	1	-	-	-	-	-
Meningioma		-	-	-	1	2	6	-	1
Lymphoma		-	-	-	-	1	1	-	-

[Table/Fig-1]: Age wise distribution of the lesions (n=67).
Abbreviations:- GBM- Glioblastomamultiforme, AO- Anaplastic oligodendroglioma, ODG- Oligodendroglioma, OA- Oligoastrocytoma, DA- Diffuse astrocytoma, BG- Brainstem glioma.

RESULTS

On analysis, it was observed that peak incidence for metastases was in the higher age group (41-50 years), so was the case for Glioblastoma multiforme (GBM) and meningiomas with peak incidence in the age group 51-60 years [Table/Fig-1]. Most common lesions were metastases, 25 cases (37.3%) followed by GBM, 22 cases [Table/Fig-2].

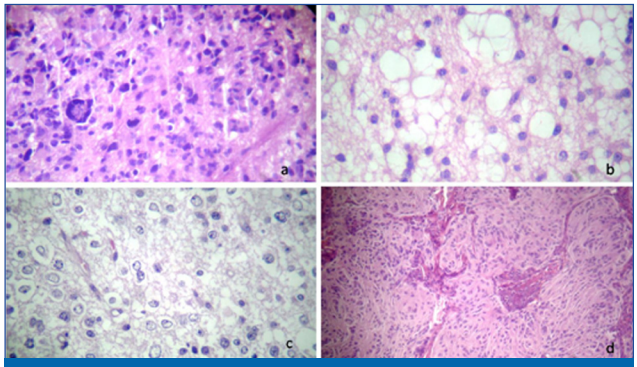
30 cases were histopathologically diagnosed as gliomas. For analysing the imaging characteristics, WHO grade I and grade II gliomas were together taken as low-grade and grade III and IV were considered high-grade [Table/Fig-3] [2,3].

Out of eight cases of low-grade gliomas, six were hyperintense on T2WI and hypointense on T1WI. Blooming on GRE imaging was seen in three. I/V contrast was given in all cases, out of which 50% showed heterogenous enhancement while 50% showed no enhancement.

Twenty two cases of high grade gliomas showed heterogenous signal on both T1WI and T2WI. Blooming on GRE imaging was seen in 15 (68.1%), diffusion restriction in 11 (50%), peripheral irregular enhancement in 16 (72%) and heterogenous enhancement in 6 (27%) cases.

Type of Lesion		No. of Lesions	Percentage
Metastases		25	37.3%
High Grade Glioma	GBM	21	31.3%
	AO	1	0.01%
Low grade Glioma	ODG	1	0.01%
	OA	1	0.01%
	DA	2	0.029%
	BG	4	0.059%
Meningioma		10	0.15%
Lymphoma		2	0.029%

[Table/Fig-2]: Distribution of patients according to Histopathological diagnosis (n=67) [M:F::37:30].



[Table/Fig-3]: a) Microphotograph of glioblastoma multiforme exhibiting high cellularity with nuclear pleomorphism and occasional giant cell (H&E400x), b) Low grade astrocytoma with proliferating astrocytes having mild nuclear pleopmorphism. Cystic change also noted (H&E400x), c) Oligodendroglioma with increased oligodendrocytes .Note the classical "fried egg" appearance (H&E400x), d) Histomorphology of meningothelial meningioma (H&E400x).

		Gliomas		Metastases	Meningioma	Lymphoma
		Low grade	High grade			
T1WI	Iso/Hypo	7/8	7/22	16/25	8/10	1/2
	Hyper	-	-	1/25	1/10	-
	Hetero	1/8	15/22	8/25	1/10	1/2
T2WI	Iso/Hypo	1/8	-	-	4/10	1/2
	Hyper	6/8	3/22	8/25	3/10	-
	Hetero	1/8	19/22	17/25	3/10	1/2
FLAIR	Iso/Hypo	1/8	-	2/25	4/10	1/2
	Hyper	6/8	3/22	6/25	3/10	-
	Hetero	1/8	19/22	17/25	3/10	1/2
Diffusion Restriction	Present	-	11/22	7/25	3/10	2/2
	Absent	8/8	11/22	18/25	7/10	-
Blooming On GRE	Present	3/8	15/22	15/25	7/10	-
	Absent	5/8	7/22	10/25	3/10	2/2
Contrast Enhance.	Homo	-	-	1/22	4/9	1/2
	Hetero	3/6	6/22	10/22	5/9	1/2
	Peripheral	-	16/22	10/22	-	-
	Absent	3/6	-	1/22	-	-

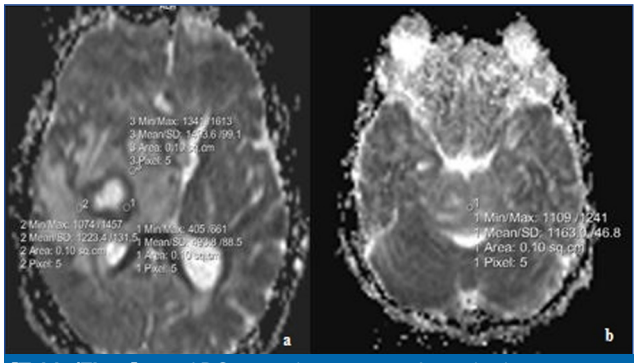
[Table/Fig-4]: Imaging characteristics of the lesions.

8 (80%) of meningiomas were isointense to hypointense on T1WI, 4 (40%) were isointense to hypointense and 3 (30%) were hyperintense on T2WI. Blooming on GRE images was seen in 7 (70%) and diffusion restriction in 3 (30%).

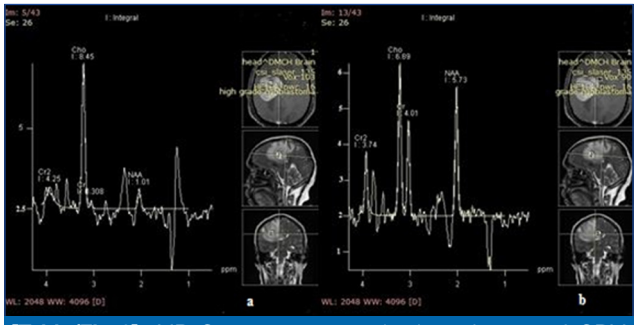
Out of 25 cases of metastases with lung being the most common primary site, 16 (64%) were isointense/ hypointense on T1WI and 17(68%) were heterogenous on T2WI. Blooming on GRE was noted in 15 (60%), diffusion restriction in 7 (28%), heterogenous enhancement in 10 (40%) and peripheral enhancement in 10 (40%) cases.

Both cases of lymphoma showed diffusion restriction and no blooming on GRE [Table/Fig-4].

Apparent diffusion coefficient (ADC) values of tumoral as well as peritumoral regions were compared. Patient with GBM and metastases had significantly lower ADC (mean= 0.73x 10-3mm2/s) in the tumoral region as compared to low grade gliomas (mean= 1.24 x 10-3mm2/s) with p value <0.0001 [Table/Fig-5]. Patients with meningioma had a wide range of ADC i.e. 0.64 to 1.2 x 10-3mm2/s (mean= 0.98x10-3mm2/s). ADC values of lymphoma (mean= 0.55 x 10-3mm2/s) were lower than that of GBM in the tumoral region.



[Table/Fig-5]: a: ADC map in a case of cerebral metastases showing irregular thick peripheral area of reduced ADC value- 0.49 with higher ADC values-1.23 and 1.41 in its peripheral T2WI hyperintense area suggesting infiltration to be less likely.
b: ADC map in a case of low grade glioma of brainstem shows higher ADC value- 1.163 in the tumor.



[Table/Fig-6]: MR Spectroscopy graphs in a A case of GBM showing markedly high choline peak with very low NAA peak and NAA/Cho ratio of 0.39. Note lipid lactate peaks at 1.33ppm [a]. Higher choline peak than NAA is seen in surrounding hyperintense signal area suggestive of tumour infiltration [b].

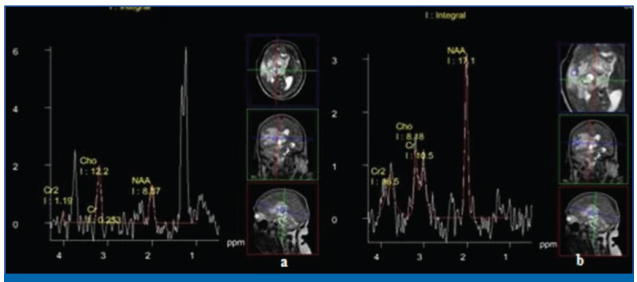
The ADC values for peritumoral areas did not differ significantly among patients with GBM, metastases and meningioma. However, peritumoral ADC values in cases of low grade gliomas were higher. Lymphoma also had slightly higher peritumoral ADC values when compared to GBM.

MR Spectroscopy was done in all cases. Statistically significant increase in choline and reduction in NAA levels was found in GBM [Table/Fig-6]. In metastases, significant reduction in the NAA levels was noted. Choline levels were also raised though not significantly [Table/Fig-6]. Reduced NAA and raised choline were also seen in cases of lymphoma [Table/Fig-7].

DW Imaging				MR Spectroscoopy									MRI diagnosis	Histopathology
ADC Values of the lesions				N-Acetyl Aspartate			Choline			Creatine				
Tumour		Peri-tumoral		Mean± SD		P value	Mean± SD		P value	Mean± SD		P value		
Mean	Range	Mean	Range	Lesion	Control		Lesion	Control		Lesion	Control			
0.73± 0.12	0.58± 0.98	1.39± 0.36	0.98± 2.3	2.05± 1.4	10.21± 6.01	<0.001 (S)	6.5± 3.84	3.15± 1.57	0.009 (S)	3.10± 1.78	3.30± 0.66	0.79 (NS)	High Grade Glioma	Glioblastoma Multiforme
0.71± 0.08	0.58± 0.89	1.36± 0.32	0.9± 1.89	1.41± 1.01	12.03± 7.88	0.0003 (S)	3.71± 1.26	2.84± 1.88	0.32 (NS)	0.72± 0.74	2.09± 0.59	0.003 (S)	Metastases	Metastases
1.24± 0.28	0.83± 1.6	1.88± 0.23	1.53± 2.21	2.11	3.86		3.48	2.56		1.89	3.45		Low Grade Gioma	Low Grade Glioma
0.98± 0.15	0.64± 1.2	1.46± 0.34	1.2± 1.73	1.05	7.23		9.51	5.43		2.58	5.41		Meningioma	Meningioma
0.55± 0.15	0.44± 0.65	1.45± 0.09	1.38± 1.52	1.03	5.48		2.81	0.98		1.42	3.41		Lymphoma	Lymphoma

[Table/Fig-7]: Comparison of ADC values, MR Spectroscopy findings, MR diagnosis with Final histopathological diagnosis.

Lipid peak was seen in 59% and both lipid and lactate peaks in 41% cases of GBM [Table/Fig-8], lipid peak was seen in14 cases while lactate peak was seen in 11cases of metastases. In low grade gliomas, lipid and lactate peaks were not noted.



[Table/Fig-8]: MR Spectroscopy graphs in a case of metastases showing higher choline peak than NAA peak and NAA/Cho ratio of 0.68. Note lipid peak at 1.33ppm [a]. Higher NAA peak than choline in the surrounding hyperintense signal area is suggestive of perilesional oedema [b].

DISCUSSION

Brain tumours constitute a major health concern because of their rising incidence. Gliomas are the most common primary brain tumours [4]. The age-standardised incidence of gliomas is about 4.7 per 100,000 person-years. The reasons for rising incidence of brain tumours are improved imaging methods of detection and better access to neurosurgical services [5]. Many studies from regional tertiary care hospitals have described detection of a large number of brain tumours ranging from 50 to more than 100 in a study period varying from 1to 3 years same as in our study. We found 67 patients of brain tumours in a study period of 18 months with gliomas constituting 32%. This higher percentage of detection of brain tumours may be because of referral of patients from various primary and secondary health centres to the tertiary hospitals for advanced neuroimaging and interventions. Similarly Goyani BR et al found 70 cases of brain tumours in a study period of two years, out of them 31.4% were metastases and 27% were gliomas [6].

G Ramparkash studied 40 histologically proven cases of primary brain tumours in a period of 18 months and found that 27% were glial and 73% were non-glial tumours [7].

Glioma

For analysing the imaging characteristics of gliomas, WHO grade I and grade II gliomas were taken together as low grade and grades III and IV were considered high grade [2,3]. In our study high grade gliomas were more common as compared to low grade.

Low grade gliomas included brainstem glioma, oligodendroglioma, diffuse astrocytoma and oligoastrocytoma while the high grade gliomas were glioblastoma multiforme and anaplastic oligodendroglioma.

Mass effect is a feature common to high and intermediate grade gliomas like GBM, oligodendroglioma and astrocytoma. Haemorrhage and gross oedema are features of GBM [8].

DW imaging:

The ADC values of the tumoral and peritumoral areas were calculated. Among all astrocytic tumours, GBMs and anaplastic astrocytomas had significantly lower ADC values as compared to low grade gliomas. The ADC values did not differ significantly between patients with GBMs versus those with metastatic tumours [9]. Increased cellular density causes restricted water movement and hence decrease in ADC values [10]

It has been reported that the accuracy, sensitivity, and specificity, respectively of ADC with conventional MRI is 90%, 88%, and 100% for discriminating high-grade from low-grade tumours. ADC values are useful for grading but not for distinguishing different tumour types of the same grade, as seen in our study [11].

We found, ADC values of lymphoma to be lower than that of glioblastoma as well as metastases and thus DW imaging could differentiate malignant lymphomas from glioblastomas and metastatic tumours using the ADC values [12]. Low ADC value favours lymphoma over gliomas [13].

MR Spectroscopy

NAA was found to be significantly reduced and choline significantly increased with NAA/Cho ratio of the order of 0.31 in cases of GBM. Comparison of these values was made with those of low grade gliomas. NAA levels were reduced and choline levels were mildly raised in low grade glioma but not that much as in GBM. NAA/Cho ratio was found to be 0.60 in low grade gliomas [14].

Spectroscopy patterns of lymphoma and GBM were almost similar. High choline levels, low NAA/Cho ratio and high Cho/Cr ratio were seen in lymphoma. A lipid lactate peak was also seen similar to GBM. It has been observed that the presence of lipid lactate peak was a consistent finding in lymphoma as compared to high grade glioma [15].

It is seen that there is an association between tumour grade and choline levels, with the high grade tumours having more choline levels [16]. As aggressive tumours have higher membrane turnover and cellular density, choline levels rise. But in certain high grade necrotic tumours, choline levels may be lower than low grade tumours due to necrosis [17].

Since tumours are commonly heterogenous, MRS values vary greatly depending on the region that is sampled [18]. Hence, the region of interest chosen for analysis has a large influence on the results.

It has been suggested that MRS should be used as an adjunct technique that may contribute to differential diagnoses that

are being considered on the basis of MRI, clinical and other information.

For differentiating solitary metastases from primary brain tumours, it has been suggested that spectrum of peritumoral area should be taken. Gliomas are often invasive and show elevated choline in surrounding tissue whereas metastases tend to be encapsulated and do not typically show higher choline outside the region of enhancement [19].

Metastatic lesions and glioblastomas nearly always show elevated lipid peaks; thus, if the lesion does not exhibit lipid signals, anaplastic glioma is more likely [20].

Usefulness of DW imaging in high-grade gliomas has been studied and it has been observed that areas with significant enhancement were markedly hyperintense on DW images and had lower ADC values than the values for non-enhancing component of tumour and peritumoral oedema. Cystic or necrotic portions of tumour were associated with the highest ADC values. On T2W, areas of hyperintensity observed in white matter could be differentiated into two patterns on the basis of findings on DW images: areas that showed higher ADC, most likely represented areas of predominantly peritumoral oedema, and areas that showed lower ADCs than those of oedema, represented areas of predominantly non-enhancing tumour. The various components of tumours – cystic, necrotic, non-enhancing and enhancing could be differentiated on DW imaging. Non-enhancing components of tumours were also differentiated from peritumoral oedema on this sequence [21].

Krabbe et al., used MRI for calculating ADC values in patients with intracranial tumours. They opined that ADC in metastases is higher than in high-grade gliomas and may be used to distinguish the two pre-operatively [22].

Meta-analysis of many studies by Wenzhi Wang et al showed that MRS is a suitable and accurate modality for discriminating brain tumours with a sensitivity and specificity of 80.58% and 78.46%, respectively [23].

Clinical Significance: Conventional MRI sequences have limitations in defining infiltration and grading of tumours, which impedes surgical resection and the post-surgical treatment. Present study suggests that using advanced MRI techniques like DW Imaging and spectroscopy allow characterisation of the tumours and peritumoral tissue, based on water diffusion and presence of metabolites. These provide clinicians a whole new perspective on improving the management of tumours and also aid differential diagnosis in ambiguous tumours.

LIMITATIONS

The major limitation of our study was small sample size especially if the data is analysed separately for separate tumours. Secondly we chose similar regions on both hemispheres for calculating metabolites between the two techniques of MRS, however minor variations in positioning of voxels cannot be excluded. Further research is needed to better define the cut off values of ADC, concentration of metabolites and their ratios in various tumours.

CONCLUSIONS

Intracranial tumours are an important indication for advanced MR imaging due to associated morbidity and mortality. We used an integrated approach of considering conventional as well as advanced MR sequences for characterizing various tumours and found it to be advantageous over conventional MR imaging. Analysis of different studies quoted in this article suggests that MRS and DWI are advantageous in grading brain tumours. We conclude that GBM and metastases are the most common intracranial tumours and are mostly heterogenous on T2W images with areas of haemorrhages, necrosis and mass effect. GBM and metastases can be differentiated from low grade gliomas on DW imaging and MRS. GBM can also be differentiated from metastases due to markedly high choline peaks and presence of peritumoral choline peak due to infiltration which is not seen in metastases. Thus DW imaging and MR spectroscopy should be incorporated into conventional MR imaging as a routine.

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