

A Study of Hippocampal T2 Relaxometry Value in Temporal Lobe Epilepsy Patient

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Received: 13th August 2023

Accepted: 30th January 2024

Published: 28th February 2024

Abstract

In the advancement of the current imaging technique for detection of mesial temporal sclerosis in temporal lobe epilepsy patient, there are multiple Magnetic resonance imaging (MRI) quantitative techniques. One of the long known to be valuable quantitative technique is T2 relaxometry where it has overall better accuracy for detection of mesial temporal sclerosis compared with the qualitative assessment only. A comparative cross-sectional study was conducted in Hospital Universiti Sains Malaysia from August 2021 to January 2023 which include 51 participants, 19 (36.5%) were temporal lobe epilepsy patient and 33 (63.5%) were control. The hippocampal T2 relaxometry was calculated for temporal lobe epilepsy patient and control. The mean T2 relaxometry reading for these groups were compared using Independent T-test. The correlation of T2 relaxometry value with age, duration of epilepsy and seizure frequency were analysed using Pearson correlation. Cohen Kappa inter-rater reliability was done for MR qualitative assessment. The participant age range was from 15 to 65 years old. Total of 23 samples were male (44.2%). The mean T2 relaxometry for epilepsy patient was higher than control. For correlation, moderate to good positive correlation was seen between the duration of epilepsy with T2 relaxometry of right hippocampus. Whereas poor positive correlation between the right hippocampus T2 relaxometry with age ($P > 0.01$), as well poor positive correlation between both hippocampus T2 relaxometry with seizure frequency ($P > 0.01$). There was one patient (5.2%) reported to be negative for mesial temporal sclerosis by qualitative assessment, but the T2 relaxometry reading however was raised. As a conclusion, T2 relaxometry sequence can be used as an adjunct to the current qualitative assessment to increase sensitivity and specificity in detecting mesial temporal sclerosis.

Keywords

Temporal Lobe Epilepsy, Mesial Temporal Sclerosis, T2 Relaxometry, MRI Epilepsy Protocol

Introduction

Epilepsy is a non-communicable disease, however it affects the patient's quality of life when seizure is uncontrolled, and this may cause psychological and socioeconomic consequences disturbance to patient and their family¹. Epilepsy affects around 50 million people worldwide and about 20-40% cases are of drug resistant case². In Malaysia, the prevalence for active epilepsy was 4.2 in 1000 population and prevalence for lifetime epilepsy was 7.8% per 1000 persons³. Temporal lobe epilepsy (TLE) is the commonest cause of focal epilepsy. It is also the commonest cause of refractory epilepsy⁴. About 70% of TLE is associated with hippocampal (mesial temporal) sclerosis- which on pathology is neuronal loss and gliosis⁵. It is estimated that up to 70% of people living with epilepsy could live seizure free if properly diagnosed and treated⁶.

MRI is one of imaging modality as a work up investigation in determining epileptic focus⁷. This is due to the non-ionizing property of this modality and superior grey white matter differentiation¹ as well as highly sensitive and specific for pathology detection⁸, compared to computed tomography (CT) and positron emission tomography-computed tomography (PET scan) which are ionizing and require radiotracer injection. Detected abnormality that is surgically approachable may be removed to cure the patient. In a recent meta-analysis involving 16,253 participants, 10,518 (65%) achieved a good outcome of surgery⁹. For temporal lobe epilepsy, the hippocampal sclerosis manifested as hyperintense signal on T2 and FLAIR with atrophic size of the hippocampus¹⁰⁻¹². However, due to the subjectivity of the visual assessment there are cases where subtle changes in the hippocampus is visually indistinguishable from normal hippocampus^{13,14}. Approximately 15% of refractory epilepsy patient does not have MRI changes of hippocampal atrophy¹⁵.

There are multiple types of quantitative MR study for detection of hippocampal sclerosis. Table 1 show summary of quantitative assessment and their sensitivity. Of these, T2 relaxometry was the most sensitive¹⁶.

Table I: Types of quantitative MRI with overall accuracy for localisation of epileptogenic area.

Types of quantitative MR	Laterizing ability (%)	Accuracy for localization of epileptogenesis area (%)	Published by
MR volumetry	71	82.4	(Chen <i>et al.</i> , 2016) and (Ercan <i>et al.</i> , 2016) ^{16,17}
MR spectroscopy (MRS)	35	Not stated	(Ercan <i>et al.</i> , 2016) ¹⁷
Diffusion tensor imaging (DTI)	42	Not stated	(Ercan <i>et al.</i> , 2016) ¹⁷
T2 relaxometry	84	94.1	(Chen <i>et al.</i> , 2016), (Hakyemez <i>et al.</i> , 2003) ^{16,18}

Study by Sato *et al.* had shown that there are four patients with negative MR finding. These patients had T2 relaxometry that was concordance with the EEG findings. Pathological findings showed one patient is confirmed to have mesial temporal sclerosis, two patients have granular cell pathology and one patient has microdysgenesis¹². There was no post-surgical outcome stated for these patients.

Up to 30% of TLE cases can be negative on MR thus compiles the presurgical workup⁴. The surgical result for patient with MR negative MTLE may not be favourable compared with hippocampal sclerosis with TLE⁴. However, we cannot miss abnormal hippocampus which appear as non-atrophic on MRI especially with the advance in 3T MR⁴. Subtle mesial temporal sclerosis (MTS) in early course of the disease is easily missed¹⁶. There are three randomized control trials have shown superiority of surgery compared to medication in refractory epilepsy¹⁹. In our centre, there are total of 11 patients have undergone epilepsy surgery since 2004 until 2017. These surgeries include anterior temporal lobectomy (ATL) with amygdalohippocampectomy (AH) and vagal nerve stimulation (VNS). The post-surgery outcome of these patients based on ILAE scores are better in ATL with AH group compared to VNS with score of 1-3 and 4-5 respectively²⁰.

The aim of this study is to improve detection of mesial temporal lobe sclerosis by implementing the use of quantitative MR method in addition to the current qualitative method. Hence to assess T2 relaxometry value in temporal lobe epilepsy patient and compare the value with the control hippocampus T2 relaxometry value.

Materials and Methods

Data collection

This is a comparative cross-sectional study which was conducted in MRI room of Hospital Universiti Sains Malaysia, Kubang Kerian. Data were collected from August 2021 until January 2023 using convenient sampling method. This study was approved by the Human Research Ethics Committee of USM (USM/JEPeM/21040319).

Participant selection

List of participants were obtained from Viarads. Patient's MR appointment date was noted. Inclusion criteria for patient were based on: (i) Clinically diagnosed temporal lobe epilepsy; (ii) Seizure free within 72 hours before MRI scan; (iii) Age 15 years old and above; whereas exclusion criteria were (i) MR show other brain pathology (tumor, infarct, etc); (ii) First trimester pregnancy. We include patient who underwent MR brain due to other reason and the scan turns out to be normal to become control. Inclusion criteria for control were based on (i) Never has seizure before; (ii) No psychiatric illness; (iii) Normal MR brain findings; (iv) Age 15 years old and above; whereas exclusion criteria were (i) Had episode of seizure before; (ii) Underlying psychiatric illness (iii) Abnormal MR brain findings; (iv) First trimester pregnancy. Participant age more than 65 years old were excluded from this study due to possibility of age-related cerebral atrophy which may become confounding factor. Total of 32 control (62.7%) were included in this study. For temporal lobe epilepsy patient, based on the inclusion criteria, a total of 19 (37.3%) were included regardless of with or without Electroencephalogram (EEG) result. The patient data such as sex, age, seizure duration and seizure frequency were obtained from their MR request form and from their medical record.

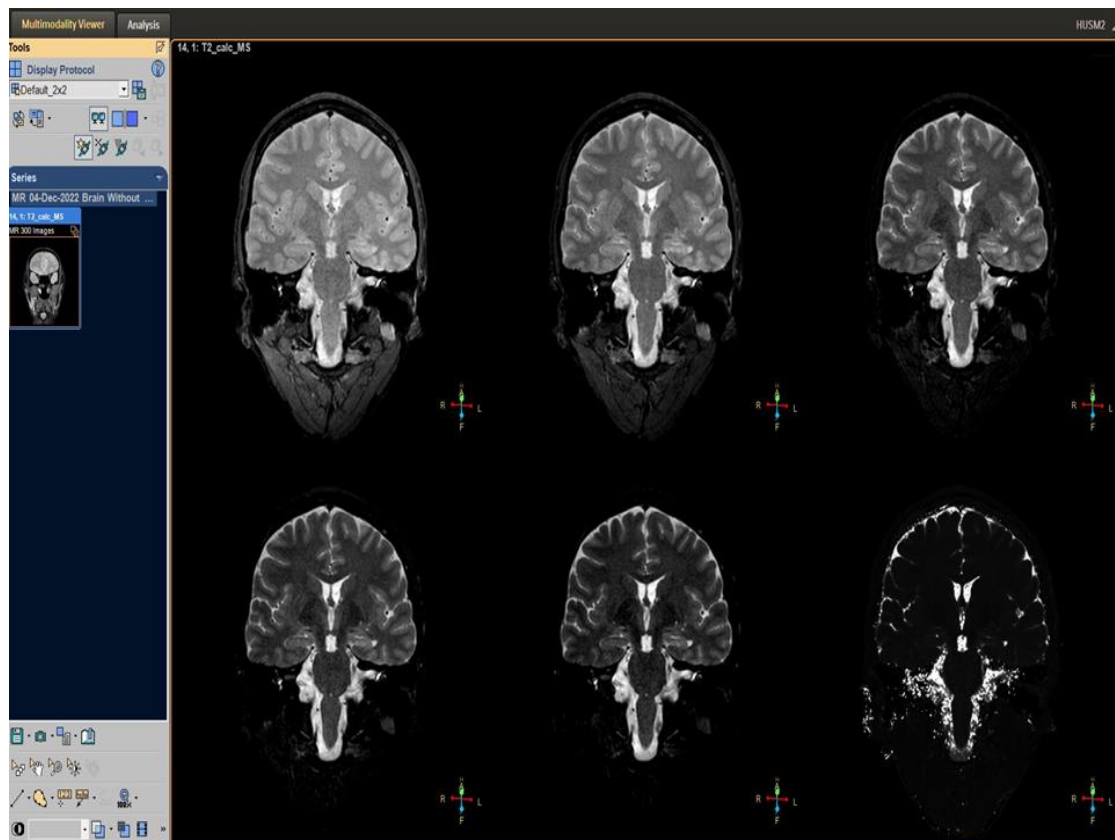
The seizure duration was documented as how many years patient had suffered from temporal lobe epilepsy. This was later calculated to get the mean in year.

The frequency of seizure was adapted from American Academy of Neurology website. Each frequency type was given group numbers as follow: (7)- Innumerable (i.e., ≥ 10 per day most days); (6)- Multiple per day (i.e., 4 days per week with ≥ 2 seizures); (5)- Daily (i.e., 4 or more days per week); (4)- Weekly but not daily (i.e., 1-3 per week); (3)- Monthly but not weekly (i.e., 1-3 per month); (2)- At least once per year, but not

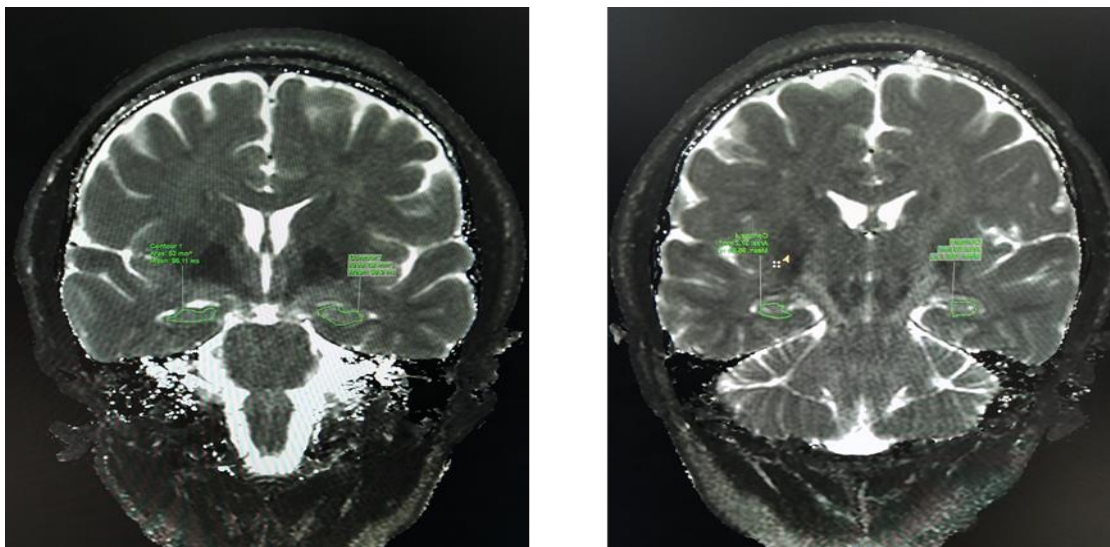
every month (i.e., 10 or fewer in past 12 months); (1)-Less than once per year; (0)- Frequency not well defined.

MR protocol

The patient and control underwent routine MRI brain sequences using Philips 3 Tesla machine (Achieva MR scanner, Best, The Netherlands). The additional T2 relaxometry sequence was added and namely T2_calc_MS sequence which: (i) Takes 5 minutes to complete the scan; (ii) Was done in coronal oblique plane perpendicular to the long axis of hippocampus; (iii) Scanned with multiple Time to Echo (TE) of 20/40/60/80/100 (Figure 1). The total duration of whole MR brain scan including the added T2_calc_MS sequence was 45 minutes to 1 hour. The calculation of T2 relaxometry was done using Philips IntelliSpace Portal 2015 workstation after the images was sent from the MR console to this workstation. The T2 map images brightness was adjusted until the hippocampus is well visualized. Then, a region of interest (ROI) was drawn at the head and body level of bilateral hippocampus trying to avoid hyperintense area to prevent contamination from the cerebrospinal fluid (CSF fluid). A higher reading is taken as the value for that side of hippocampus. The reading is validated by senior radiologist who had more than 10 years' experience. The qualitative diagnosis was made by the working radiologist on the day of scan. Another radiologist will interpret the MR image qualitatively and gave their diagnosis. Inter-rater reliability will be done with Cohen statistics.



1a



1b

Figure 1a: Above is MR Images with different TE. Upper images from the left to right TE 20/40/60 ms. For second row image from left to right TE are 80/100 ms. On the right lower most image is The T2 map image. Red arrow show tools for ROI placement at the hippocampus which will be done on the T2 map image.

Figure 1b: Above are images of T2 maps: ROI placement on the head of bilateral hippocampus will generate mean relaxation time (in ms) of the hippocampus (Left is at the level of head hippocampus, right is at level of body).

Data Analysis

All data were analysed using Statistical Product and Service Solutions (SPSS) for Mac, IBM Corp.© (Version 28). The descriptive statistics were used for discrete variables (sex, age, and type of participants) and was presented as n=frequency (%). Independent t-test was used to compare the mean of T2 relaxometry value between control and patient. Statistical analyses were presented in tables. Pearson Correlation Coefficient was used to determine the correlation between the age, seizure frequency and seizure duration with the T2 relaxometry value. The level of significance was set at $P < 0.05$. Statistical analyses were presented in tables.

Results

A total of 51 participant underwent the additional T2_calc_ MS sequence, 19 (37.3%) were temporal lobe epilepsy patient and 32 (62.7%) were control. The age range is from 15 to 65 years old. Total of 22 participants were male (43.1%) and 29 participants were female (56.7%). There were six participants in paediatric age group (11.8%). Table II shows the summary of participants demographic. The mean duration of suffering epilepsy for all temporal lobe epilepsy patient was 9.42 years. Majority of patient (11 out of 19) had monthly attack which is one to three episode per month.

Table III show the comparison of mean T2 relaxometry value for epilepsy patient and control which show significantly higher T2 relaxometry value in patient compared to control ($P < 0.001$). The value was also higher in the right hippocampus than left hippocampus for patient and control. For temporal lobe epilepsy patient, the reading for right and left hippocampus were 110.13 (10.51) ms and 107.15 (9.43) ms

respectively. Meanwhile for control the reading for right and left hippocampus were 99.54 (4.00) ms and 97.00 (3.46) ms respectively.

Table IV shows the correlation between T2 relaxometry of bilateral hippocampus with age, duration of epilepsy and seizure frequency. There was moderate to good positive correlation between right hippocampus T2 relaxometry with duration of epilepsy ($P < 0.05$). However, there was negative correlation between left hippocampus T2 relaxometry with duration of epilepsy. Poor positive correlation between the right hippocampus T2 relaxometry with age ($P > 0.01$), as well poor positive correlation between both hippocampus T2 relaxometry with seizure frequency ($P > 0.01$). Negative correlation between T2 relaxometry of left hippocampus with age ($r = -0.167$).

There was one patient (5.2%) whom was qualitatively reported as negative for mesial temporal sclerosis, however the T2 relaxometry reading was raised in right side which was consistent with EEG finding.

Table II: Type of participant, sex, age group for all participant and seizure frequency as well as the mean duration (years) of suffering epilepsy for temporal lobe epilepsy patient.

Variable	n(%)
Type of participant (n=51)	
Control	33(63.5)
Patient	19(36.5)
Sex (n=51)	
Female	29(55.8)
Male	23(44.2)
Age (n=51)	
Paediatrics	6 (11.8)
Adult	45(88.2)
Seizure frequency (n=19)	
0- Frequency not well defined	0(0)
1- Less than 1 per year	5(26.3)
2- At least 1 per year	1(5.3)
3- 1 to 3 times per month	11(57.9)
4- 1 to 3 times per week	1(5.3)
5- 4 or more days per week	0 (0)
6- Multiple time per day	1(5.3)
7- Innumerable	0 (0)
Mean duration of epilepsy in years (n=19)	9.42

Seizure frequency was adapted from the American academy of Neurology and given group number based on the frequency of seizure from 0 to 7 accordingly.

Table III: The comparison of Mean T2 relaxometry value for hippocampus in control and epilepsy group (n=51).

Variable	Control Mean (SD) in ms	Epilepsy Mean (SD) in ms	Mean difference (95% CI)	P- value
T2 relaxometry of hippocampus	Right : 99.54 (4.00)	Right : 110.13 (10.51)	-10.59(-14.74,- 6.44)	<0.001
	Left : 97.00 (3.46)	Left :107.15 (9.43)	-10.15(-13.84,- 6.46)	<0.001

Independent t-test applied; Normality assumption and equal variance assumption were fulfilled.

Table IV: Correlation of T2 relaxometry value with age, duration of epilepsy and seizure frequency among epilepsy group (n=19), presented with r value

	Right hippocampus	Left hippocampus
Age	0.219	-0.167
Duration of epilepsy	0.511*	-0.044
Seizure frequency	0.054	0.120

*. Correlation is significant at the 0.05 level (2-tailed). Pearson correlation applied. Normality assumption fulfilled.

Cohen kappa inter-rater reliability for hippocampus qualitative assessment showed almost perfect agreement between reader one and reader two with value of 0.87.

Discussion

Hippocampal T2 relaxometry is a quantitative assessment method for and is used to differentiate between normal from abnormal tissue²¹. The use had been shown to be helpful in subtle hippocampal changes evaluation and was studied mostly among adult population. There was no normative value as reference for hippocampus in paediatric population. In this study paediatric population were also included. We include those age from 15 years to 65 years old. There were total of 6 (11.8%) paediatrics that were included with parental consent to take part. The paediatric age selection is to determine whether there is any correlation between age and T2 relaxometry value as well as to get normative value of T2 relaxometry. From overall temporal lobe epilepsy surgery, 71.9% were adult and 23% were paediatrics²². However, the outcome of seizure freedom is better in paediatric than adult. Seizure freedom is a seizure free state prompting to discontinuation of antiepileptic drug after temporal lobe epilepsy surgery. Study by Barba et al. confirmed that a younger age of seizure onset and surgery was associated with withdrawal of AED. We still chose to include adult as majority of our participants because from our centre experience, majority of those underwent epilepsy surgery were adults²⁰.

In our study, as reported by previous studies, there is a difference in the mean T2 relaxometry value between control and temporal lobe epilepsy patient. The control had lower T2 relaxation value compared to epilepsy patient^{12,14-16,23}. The increased in T2 relaxometry value for temporal lobe epilepsy patient is correlated with the dentate gliosis, neuronal cell loss as well as gliosis and dispersion of the granular cell layer²⁴. Our T2 relaxometry value for control was 99.54 (4.00) ms and 97.00 (3.46) ms for right and left hippocampus respectively. This result was almost similar to study done in China by Chen et al. and study done in Australia by Briellman et al, where their value was 98.38 (3.96) ms and 98 (2.7) ms for right hippocampus and 98.80 (3.91) ms and 97 (3.5) ms for left hippocampus respectively^{16,25}. In these studies, they were also using a 3-Tesla (3T) machine which may affect the similarity in our result. However, there are few more studies using similar 3T MR machine such as study by Sato et al., and Winston et al., but their normative value for control were higher than our value and hence there is overlapping between their T2 relaxometry value for control and T2 relaxometry value for our patient population. The difference might be due to different age range for control such as in study by Sato et al, the age range is 22 to 44 years old whereas our study is ranging from 15 to 65 years old. In brain development process, the myelination process will contribute to the decrease in the T1 and T2 value hence affecting the relaxometry value²⁶. In paper published by Hagiwara et al, the measurement of T2 relaxometry for white matter and grey matter across age had shown that the value had quadratic changes according to age and stayed plateau or decrease until around 60 years old. Based on these we conclude that the wider range of our participant age had effect

on the difference in our mean T2 relaxometry value compared to study done by Sato et al where their participant age range is narrower. Although this study doesn't include hippocampus in the measurement, due to the anatomical component of hippocampus consist of bilaminar grey matter structure²⁷, it is likely that hippocampus will show the same result with the rest of grey matter. In the study done by Winston et al. they use automated delineation of the hippocampus whereas our study used manual region of interest (ROI) delineation. This is because manual ROI delineation is limited in size to avoid CSF, however in automated hippocampal segmentation, the cross-sectional area of slice can extend to 50 mm² but later the CSF contamination will be minimized by eroding the CSF²⁴. In this technique, there is still high likely that there is residual CSF contamination with the automated ROI delineation hence resulting in difference mean hippocampus T2 relaxometry value compared with our study. The other possibility for the difference in T2 relaxometry value can also be due to potential instrument difference.

For patient and control, our study showed right hippocampus had higher T2 relaxometry value compared to the left hippocampus. This may be attributed to the hippocampus size variation where the right hippocampus is slightly larger than the left hippocampus²⁸. It is also reported that there is right-greater-than-left asymmetry of hippocampus in the right handed individual²⁹ which can be another reason for the higher right hippocampus reading.

There were total 19 temporal lobe epilepsy patients in this study. Eighteen patients with abnormal hippocampus on visual assessment had high T2 relaxometry value. However, there was one patient (5.2%) from the epilepsy group had abnormal T2 relaxometry value, but visual assessment failed to detect the hippocampal abnormality. This has also been observed in study by Sato et al, and confirmed by histopathological result of hippocampal sclerosis. This may occur when there is absence of hippocampal atrophy due to counterbalance of the volume deficit by enlarge cells¹². The enlarged cells occur as the reactive astrocyte contains higher cytoplasm and intracellular water, thus counterbalance the volume deficit induced by neuronal cell loss. Thus, this may not be detected by visual assessment but detected with T2 relaxometry.

For correlation between T2 relaxometry with age, duration of epilepsy and seizure frequency, there was only one study had made correlation and the result was negative¹³. Our study showed that there is moderate positive correlation between the duration of epilepsy the right hippocampus T2 relaxometry value. The age and seizure frequency has no correlation with hippocampal T2 relaxometry similar with the previous study¹³. However, upon further comparing between our study and that study done by Grunewald et al, there is difference, in which our study had made correlation between years of suffering epilepsy, instead of correlation between duration of each epilepsy episode with T2 relaxometry value. It is not clearly stated in that study on how the correlation made with the age and seizure frequency hence we unable to compare these two parameters. Hence our study could be the first study which had done correlation between T2 relaxometry with age, duration of epilepsy and seizure frequency

Conclusion

Our study showed higher hippocampal T2 relaxometry value in epilepsy patient compared to control. In a case of clinically diagnosed temporal lobe epilepsy based on clinical history, but MRI show no intracranial pathology such as tumour or focal cortical dysplasia, the T2_calc_MS sequence (T2 relaxometry) can be added during MR brain for detection of hippocampal abnormality by quantitative measures.

Acknowledgements

Grant provider under PPSP, HUSM, with the help we were able to enrol two additional participants. This study has not been presented or published in any journal or symposium.

Conflict of Interest Disclosure

None to declare

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