



Case report

Stereo-electroencephalographic seizure localization in patients with mesial temporal sclerosis: A single center experience

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ABSTRACT

Objective: Epilepsy patients with mesial temporal sclerosis (MTS) on imaging who are drug-resistant usually undergo epilepsy surgery without previous invasive evaluation. However, up to one-third of patients are not seizure-free after surgery. Prior studies have identified risk factors for surgical failure, but it is unclear if they are associated with bilateral or discordant seizure onset.

Methods: In this retrospective case series, we identified 17 epilepsy patients who had MRI-confirmed MTS but received invasive stereo-EEG (SEEG) evaluation before definitive intervention. We analyzed their presurgical risk factors in relation to SEEG seizure onset localization and MRI/SEEG concordance.

Results: SEEG ictal onset was concordant with MTS localization (i.e. seizures started only from the hippocampus with MTS) in 5 out of 13 patients with unilateral MTS (UMTS) and in 3 out of 4 patients with bilateral MTS.

No statistically significant association regarding concordance of SEEG ictal onset and MTS location was found in patients with such risk factors as a history of non-mesial temporal aura, frequent focal to bilateral tonic-clonic seizures, prior viral brain infection, or family history of epilepsy. Nine out of 13 UMTS patients had resective surgery only, 5 out of 9 (56%) have Engel class I outcome at most recent follow-up (median 46.5 months, range 22–91 months). In Engel class I cohort, the SEEG ictal onset was concordant with MTS location in 3 out of 5 patients, and 2 patients had ipsilateral temporal neocortical ictal onset.

Conclusions: Our findings suggest that patients with MTS might have discordant SEEG ictal onset (in 61.5% patients with UMTS in presented cohort), which may explain poor surgical outcome after destructive surgery in these cases.

Significance: Although no statistically significant association was found in this under-powered study, these findings could be potentially valuable for future meta-analyses.

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1. Introduction

Patients with drug-resistant epilepsy related to unilateral mesial temporal lobe sclerosis (UMTS) on imaging are considered excellent surgical candidates, with > 65% achieving seizure freedom for at least one year after destructive surgery. (Engel et al., 2003) Thus, patients with UMTS often do not undergo invasive stereo-electroencephalography (SEEG) evaluations prior to surgery, unless seizure semiology, MRI lesion localization, and/or scalp EEG ictal onset are discordant. (Paredes-Aragon et al., 2022) On the other hand, patients with bilateral mesial temporal lobe sclerosis (BMTS) may undergo SEEG to confirm the seizure onset

zone, and receive bilateral hippocampal responsive neurostimulation (RNS) afterwards. (Geller et al., 2017).

Presence of generalized convulsions and bilateral MRI abnormalities are considered as the risk factors for poor response to destructive surgery such as anterior temporal lobectomy (ATL) and selective amygdalohippocampotomy via laser interstitial thermal therapy (ahLITT) in mesial temporal epilepsy. (Kuzniecky et al., 1999, Jeha et al., 2006, Jehi et al., 2015) Yet, little is known about how these risk factors contribute to precise electrographic seizure localization in MTS, which plays an important role in surgical planning and prognosis. (Arévalo-Astrada et al., 2021) In this case series, we retrospectively reviewed epilepsy patients without history of prior destructive surgery who had MRI evidence of UMTS or BMTS and underwent SEEG evaluation. We analyzed SEEG localization results in relation to epilepsy risk factors and seizure semiology, and epilepsy surgery outcomes in this patient cohort to define biomarkers associated with surgical failures in patients with MTS.

2. Methods

2.1. Patients

This is a retrospective case series approved by the University of Texas Southwestern Medical Center Institutional Review Board. We screened 179 subsequent adult SEEG implantations and found 17 patients who met the following inclusion criteria: (1) presence of UMTS or BMTS on MRI, (2) no prior destructive epilepsy surgery; (3) underwent SEEG evaluation with stereoelectrodes sampling the hippocampus or hippocampi with MTS, and (4) had ≥ 18 months of follow-up after initial intervention (destructive surgery, RNS, or medical management).

2.2. SEEG evaluation

SEEG implantation was performed as previously described. (Durica et al., 2023) Postoperatively, all SEEG segments were analyzed by two epileptologists, who determined the location of ictal onset. The ictal onset was defined as repetitive spike discharges, or rhythmic fast waves.

SEEG concordance with MTS was defined as SEEG ictal onset recorded only from the hippocampus with MTS seen on MRI.

2.3. Surgical treatments

Recommendations for surgery were made at a multidisciplinary conference after SEEG evaluation. Patients who underwent surgical treatments received either ATL, ahLITT, extra-temporal lesionectomy, resection plus RNS, or RNS implantation only.

2.4. Surgical outcomes

Seizure outcomes at the most recent follow-up were classified according to the Engel Epilepsy Surgical Outcome Scale. (Engel 1993) For patients who had RNS implantation or medical management, we calculated their percentage reduction in seizure frequency.

2.5. Statistics

Statistical analysis was performed with MATLAB R2022a software (The MathWorks Inc., Natick, Massachusetts). Group differences were compared using Fisher's Exact Test, and two-sided $p < 0.05$ was taken as significant.

3. Results

3.1. Patient characteristics

Patient characteristics are summarized in Table 1. Reasons for SEEG evaluation include presence of other brain lesions (10/17), discordant seizure semiology (12/17), discordant scalp EEG (11/17, defined as presence of scalp EEG ictal onset outside of the temporal or frontotemporal lobe ipsilateral with MTS as seen on MRI), and a combination of these factors (12/17).

3.2. MRI findings

Thirteen patients had MRI evidence of UMTS (4 left MTS). Four patients had MRI evidence of BMTS. Additional lesions were identified on MRI in 10 patients (Table 1).

3.3. SEEG ictal onset localization

SEEG ictal onset was concordant with MTS localization in 5 out of 13 patients and discordant in 8 patients with UMTS (Table 1).

SEEG ictal onset was concordant with BMTS localization in 3 out of 4 patients, and one patient had ictal onset of clinical seizures from the left posterior temporal/parietal cortex, and bilateral mesial temporal subclinical seizures.

Only 1 out of 10 patients with additional brain lesion(s) had SEEG ictal onset from such a lesion.

3.4. Discordance risk factors analysis

Analysis of risk factors contributing to SEEG/MTS discordance and presence of bilateral ictal onset on SEEG are described below. P values are summarized in Table 2.

3.4.1. Non-mesial temporal auras

Eight out of 17 patients (7-UMTS, 1-BMTS) had non-mesial temporal auras (e.g., visual, auditory, and somatosensory), and 6 of them (75 %) had SEEG/MTS discordant ictal onset. Interestingly, 4 of these 6 patients who had non-mesial temporal aura and SEEG/MTS discordant ictal onset had concordant scalp EEG ictal onset localization.

3.4.2. Frequent focal to bilateral tonic-clonic seizures

Five out of 13 patients with UMTS had frequent (>1 /year) focal-to-bilateral tonic-clonic seizures (fFBTC), and 4 (80 %) of them had SEEG/MTS discordant ictal onset, despite scalp EEG showing ictal onset ipsilateral to MTS. Overall, six out of 8 patients with reported fFBTC had bilateral ictal onset on SEEG ($p = 0.057$, Table 2).

3.4.3. History of viral and bacterial brain infection

Three out of 17 patients (1-UMTS, 2-BMTS) had history of viral encephalitis, all three had bilateral temporal SEEG ictal onsets, and 2 (67 %) of them had SEEG localization discordant with MTS location (Table 1). Three other patients in the cohort had prior history of bacterial meningitis/encephalitis, all three had concordant MTS/SEEG ictal onset.

3.4.4. Family history of epilepsy

Four out of 13 patients in UMTS group had positive family history of epilepsy. None of them had unilateral mesial temporal SEEG ictal onset and none were concordant with MRI localization. However, scalp ictal EEG onset was concordant with MTS in 2 of these 4 patients.

Table 1
Patient demographics, SEEG seizure localization, and outcome.

Patient ID	Race, Ethnicity, Gender, Handedness	Epilepsy onset age (years) and duration until SEEG (years)	History of non-MTLE aura, Y/N	Viral (V), bacterial (B) encephalitis or meningitis, or neither (N)	Frequent GTC (at least every year), Y/N	Family history of epilepsy, Y/N	Scalp EEG ictal onset, habitual seizures	SEEG ictal onset, habitual seizures	MRI findings	MTS/ SEEG concordance, Y/N	Surgery or other intervention; surgical pathology	Outcome at most recent follow-up (Engel class or % reduction in seizure frequency)* / follow-up duration since surgical intervention
Destructive surgery only												
1	White, Non-Hispanic, Fe, L	16, 10	N	N	N	N	L TPO	IMT	L MTS, LP encephalomalacia, L STG atrophy	Y	L ATL; MTS	IA, 30 mo
2	White, Hispanic, M, R	27, 4	Y	N	N	N	R FT	IMT	R MTS	Y	R ATL; MTS	IA, 31 mo
3	White, Non-Hispanic, M, R	2, 35	N	N	Y ^{***}	N	LT, non-localizing	IMT	L MTS	Y	ahLITT; NA	IA, 63 mo
4	White, Non-Hispanic, M, R	0.5, 24.5	N	N	N	Y	CS: R FC; SS: RT	ILT	R MTS, LP MCD	N	R ATL; normal neocortex, MTS	IA, 30 mo
5	White, Hispanic, Fe, R	7, 17	Y	N	N	N	L TP	IMT, ILT	L MTS, L FP encephalomalacia	N	L ATL; MTS	IB, 91 mo
6	White, Hispanic, Fe, R	8, 28	N	B	N	N	LT, non-localizing	IMT	L MTS	Y	L ATL; MTS	II, 22 mo
7	White, Non-Hispanic, M, R	51, 9	Y	N	N	N	LT, L TP, LF, Cz, non-localizing	CS - IET; SS - IMT	L MTS, L FP encephalomalacia	N	L mesial frontal resection; normal	II, 55 mo
8	White, Non-Hispanic, Fe, R	17, 2	Y	N	Y	N	RT	IMT, BLT	R MTS	N	R ATL; MTS	III, 57 mo
9	White, Non-Hispanic, M, R	8, 42	Y	N	Y	Y	RT	BMT	R MTS, TS	N	R ATL, then R parietal resection; R MTS, TS	IV, 52 mo
RNS												
10	White, Non-Hispanic, Fe, R	35, 2	Y	V	Y	Y	L PO	BMT	BMTS, L fronto-parietal meningioma	Y	RNS; NA	0 %, 66 mo
11	White, Hispanic, Fe, R	3, 45	N	B	N	N	Non-localizing/ non-lateralizing, L FT	BMT	BMTS, Bilateral frontal encephalomalacia	Y	RNS; NA	66 %, 68 mo
12	Black/ African American, Non-Hispanic, Fe, R	0.5, 12	Y	N	Y	N	RT	BMT	R MTS, Hypoplasia of the R thalamus, subependymal nodularity along the R lateral ventricle	N	RNS; NA	0 %, 36 mo
13	White, Hispanic, M, R	36, 5	N	V	Y	N	RT, LT, R PO, RF	CS - ILT, IET; SS - ILT, BMT	BMTS	N	RNS; NA	100 %, 27 mo
14	Asian, Non-Hispanic, M, R	30, 27	N	B	N	N	RT, LT, non-localizing	IMT	R MTS, LP encephalomalacia	Y	Concurrent R ATL and RNS; MTS	100 %, 26 mo
15	White, Non-Hispanic, M,	8, 14	Y	N	Y	Y	RT	ILT, IET	R MTS, R MTG MCD	N	1. R posterior temporal neocortical	0 % ^{**} , 41 mo

Table 1 (continued)

Patient ID	Race, Ethnicity, Gender, Handedness	Epilepsy onset age (years) and duration until SEEG (years)	History of non-MTLE aura, Y/N	Viral (V), bacterial (B) encephalitis or meningitis, or neither (N)	Frequent GTC (at least every year), Y/N	Family history of epilepsy, Y/N	Scalp EEG ictal onset, habitual seizures	SEEG ictal onset, habitual seizures	MRI findings	MTS/SEEG concordance, Y/N	Surgery or other interventional, surgical pathology	Outcome at most recent follow-up (Engel class or % reduction in seizure frequency)/follow-up duration since surgical intervention
	R										and right insular resection, 2. R ATL, 3. RNS; normal, MTS	
Medical management												
16	White, Non-Hispanic, Fe, R	26, 10	N	V	N	Y	RT, LT	BMT	R MTS	N	Autoimmune treatment (monthly IVIG) ^{****} ; NA	88%, NA
17	White, Hispanic, M, R	1, 37	N	N	Y	Y	RT, LT	BMT	BMTS	Y	Medical management; NA	98%, NA

Abbreviations: ATL - anterior temporal lobectomy; BLT - bilateral neocortical temporal; BMT - bilateral mesial temporal; CS - habitual clinical seizures; Cz - central vertex; F - frontal; FC - fronto-central; Fe - female; FCD - focal cortical dysplasia; FT - frontotemporal; GTC - generalized tonic-clonic seizure; IET - ipsilateral extratemporal; ILT - ipsilateral lateral temporal; IMT - ipsilateral mesial temporal; IVIG - intravenous immunoglobulin; L - left; ahlJTT - selective amygdalohippocampotomy via laser interstitial thermal therapy; M - male; MCD - malformations of cortical development; MTG - middle temporal gyrus; MTLE - mesial temporal lobe epilepsy; MTS - mesial temporal sclerosis; NA - not applicable; P - parietal; PO - parieto-occipital; R - right; RNS - responsive neural stimulation; SEEG - stereo-EEG; SS - subclinical seizures; STG - superior temporal gyrus; T - temporal; TBI - traumatic brain injury; TP - temporoparietal; TPO - temporoparietooctipital; TS - tuberous sclerosis.

*Engel outcomes for patients receiving resective surgery only, % seizure reduction for patients receiving RNS.

** This patient initially received resective surgery, but received RNS implantation 1 year and 5 months later.

***Focal to bilateral tonic-clonic seizures never recorded in EMU.

**** Autoimmune disease was diagnosed after SEEG evaluation.

3.5. Surgical and nonsurgical outcomes

Ten out of 13 UMTS patients had destructive surgery as the first therapeutic surgical procedure (7-ATL, 1-ahlJTT, 1-posterior temporal neocortex and insula resection, 1-frontal lesionectomy), median follow-up 46.5 (22–91) months. After initial resection, 2 out of 10 UMTS patients (both had discordant SEEG ictal onset) received a second resection, one of them then received a third resection and RNS.

In patients who received destructive surgery, 5 (56%) were Engel I outcome at the most recent follow-up (4 ATL, 1 ahlJTT), 2 are Engel II (1 ATL, 1 frontal lesionectomy), 1 is Engel III (ATL), and one is Engel IV (ATL followed by extratemporal lesionectomy in patient with bilateral mesial temporal seizures and tuberous sclerosis). One patient received initial destructive surgery followed by RNS as described above. SEEG/MTS was concordant in four out of ten patients who received destructive surgery. Three out of four patients with SEEG/MTS concordance are Engel I at last follow-up, and one out of four has Engel II outcome. All patients with SEEG/MTS discordance had seizure relapse after resection. In Engel I cohort, SEEG/MTS was discordant in 2 out of 5 patients, but the ictal onset regions were deemed to be within the resected cortex.

In the 5 patients with Engle I outcome, 1 had history of fFBTC, 1 had family history of epilepsy, and none had history of viral or bacterial brain infections. Bilateral SEEG ictal onset were present in none of the patients with Engel I outcome.

Seven patients did not receive initial destructive surgery, including all four patients with BMTS and three patients with UMTS. Three patients with BMTS received RNS only and 1 received medical management. Of the three remaining UMTS patients, one had bilateral ictal onset on SEEG and received RNS, one had an ictal onset concordant with MTS localization, but also had continuous bilateral mesial and neocortical temporal interictal activity and received ATL and bilateral temporal RNS, and one had autoimmune etiology confirmed after SEEG evaluation and is managed medically. Percentage of seizure frequency reduction for these patients are listed in Table 1.

3.6. Response to RNS therapy

In the RNS cohort, 3 out of 6 patients had the same seizure frequency at the last follow-up, but their seizure duration and severity decreased compared to their pre-operative baselines (Table 1, Patients 10, 12, and 15). Two out of three “poor responders” had bilateral mesial temporal SEEG ictal onsets and are receiving bi-hippocampal RNS therapy. The other “poor responder” had unilateral MTS and ictal SEEG onsets within the ipsilateral right posterior temporal neocortex and right insula. He had resections of the right temporal neocortex, insula, and right ATL, and had RNS leads placed over the posterior resection edge. All three “poor responders” had fFBTC before epilepsy surgery which could potentially be a risk factor of less favorable response to RNS therapy. Two patients (Patient 13 and 14) had 100% seizure frequency reduction, and one (Patient 11) had 66% reduction of seizure frequency. In these three “good responders”, only Patient 13 reported fFBTC pre-operatively. Patients 11 and 13 both received bi-hippocampal RNS therapy. Patient 14 had right MTS and his SEEG ictal onset was concordant with MTS but with frequent bilateral mesial and neocortical temporal interictal spikes. He underwent right ATL and RNS leads placement to the right temporal lobe resection edge and left hippocampus. His RNS only captured one seizure that started from the right temporal lobe resection edge, which was a result of missed anti-seizure medications.

Table 2
Risk factor vs. discordant or bilateral SEEG seizure localization.

		SEEG and MRI Concordant (N = 8)	SEEG and MRI Discordant (N = 9)	P value	Unilateral SEEG ictal onset (N = 9)	Bilateral SEEG ictal onset (N = 8)	P value
Non-mesial temporal auras	Y	2	6	0.15	4	4	1
	N	6	3		5	4	
>1/year focal to bilateral tonic-clonic seizures	Y	3	5	0.64	2	6	0.057
	N	5	4		7	2	
History of viral infection of the brain	Y	1	2	1	0	3	0.082
	N	7	7		9	5	
History of bacterial infection of the brain	Y	3	0	0.082	2	1	1
	N	5	9		7	7	
Family history of epilepsy	Y	2	4	0.62	2	4	0.33
	N	6	5		7	4	

4. Discussion

In this study, we present a cohort of 17 patients with MTS who required SEEG for further seizure localization. We found SEEG/MTS concordance in patients with MTS who required SEEG evaluation could be predictive of favorable epilepsy surgery outcome. Further, patients with non-mesial temporal auras, fFBTC, viral brain infections, or family history of epilepsy were more likely to have discordant SEEG findings or bilateral SEEG ictal onset and may be poor candidates for destructive surgery, but these findings were not statistically significant.

Prior studies have associated visual and somatosensory auras with poor surgery outcomes in mesial temporal lobe epilepsy (mTLE). (Ferrari-Marinho et al., 2012, Perven et al., 2015) Presumably, the presence of these auras indicate extratemporal localization of seizure activity, which cannot be eliminated with ATL or aHLITT. (Ferrari-Marinho et al., 2012) Indeed, we found that SEEG evaluations in these patients often resulted in discordant localization to MRI findings. Similarly, focal to bilateral tonic-clonic seizures were associated with poor surgical outcomes in mTLE likely due to bilateral or extended epileptogenic regions that are unamenable to destructive surgery. (Janszky et al., 2005, Jeha et al., 2006) We found that SEEG evaluation in patients with fFBTC often resulted in discordant and/or bilateral seizure localization. Our results agree with previous findings and advocate for SEEG evaluation before definitive surgical management in these patients.

In our cohort, decision to proceed with surgery in 2 patients (Table 1, subjects 8 and 9) who ultimately had poor outcomes when there was lack of SEEG/MTS concordance as well as the presence of 2 risk factors (non-mesial temporal aura, fFBTC) known to predict a worse surgical outcome was based on previous study reported improvement of quality of life after resective surgery in 27% of patients despite of persistent seizures (Sheikh et al., 2019).

Patients with a history of viral encephalitis were found to be less likely to achieve seizure freedom after surgery than those with a history of bacterial meningitis. (Ramantani and Holthausen, 2017) Here, we observe that all the patients in our cohort with prior viral brain infections had bilateral ictal onset on SEEG, which suggests that viral pathogens may cause diffuse brain damage and subsequent bilateral epileptogenicity, rendering these patients poor surgical candidates. (Ramantani and Holthausen, 2017, Liu et al., 2019).

Family history of epilepsy has not been consistently associated with poor surgical outcomes in mTLE. (Asadi-Pooya et al., 2016, Pereira Dalio et al., 2022) The genetics of mTLE is complex, and rare genetic variants did not appear to influence surgical outcomes. (Perucca et al., 2023) In our cohort, genetic analysis was only carried out in one patient, who was found to have one benign variant

in KCNH5 and one variant of uncertain significance in SATB2. (Rosenfeld et al., 2009, Happ et al., 2023) This patient was deemed a surgical candidate and underwent ATL with Engel III outcome at most recent follow-up. Overall, we did not observe a strong trend for the association of family history of epilepsy with bilateral or discordant SEEG localization. Studies with extensive genetic analysis are required in the future to identify specific genes that may influence epileptogenesis and response to surgery in mTLE.

An interesting finding in this series is that only 1 out of 10 patients with additional brain lesions had SEEG ictal onset from this lesion. Although our series is small, this could suggest that SEEG may not be necessary or helpful if the presence of an additional lesion is the only indication for SEEG and all other findings suggest concordance with MTS.

We observed that only 5 out of 9 (56%) patients with destructive surgery achieved Engel I outcome at last follow-up, which was slightly lower than previously reported outcomes in all MTS patients. (Engel et al., 2003) It is known that the need for invasive EEG evaluation by itself is associated with poor response to surgery in MTS patients. (Jeha et al., 2006) Our results in this complex population suggest that further SEEG/MTS concordance may help select good candidates for destructive surgery.

Interestingly, the response to RNS appears to be extreme in one direction or the other – 100% of seizure frequency reduction in 2 patients, and 0% reduction in 3 others - with only 1 patient having the more expected response (66% reduction). All “poor responders” have fFBTC before epilepsy surgery which potentially could be a risk factor of less favorable response to RNS therapy, although these patients reported improvement in seizure frequency and severity.

The biggest limitation in our study is the small sample size; we are underpowered to determine any statistically significant associations. However, since patients with UMTS usually proceed to surgery without invasive evaluation, our cohort of patients who have all received SEEG evaluation represents a minority of MTS patients. Another limitation is the retrospective, single-center design, which may limit the generalizability of our results. Future multicenter, prospective studies are needed to address these limitations.

5. Conclusion

In conclusion, our study demonstrates that patients with UMTS and concordant scalp EEG ictal onset might have discordant SEEG ictal onset, which may explain poor surgical outcome after destructive surgery in these cases. History of non-mesial temporal aura, fFBTC, prior viral brain infection, or family history of epilepsy could raise the concern for higher probability of surgical failure, and these findings could be potentially valuable for future meta-analyses.

CRediT authorship contribution statement

Bill Zhang: Data curation, Formal analysis, Investigation, Validation, Visualization, Writing – original draft, Writing – review & editing. **Irina Podkorytova:** Conceptualization, Data curation, Methodology, Project administration, Resources, Supervision, Investigation, Validation, Visualization, Formal analysis, Writing – review & editing. **Ryan Hays:** Data curation, Formal analysis, Resources, Writing – review & editing. **Ghazala Perven:** Data curation, Formal analysis, Resources, Writing – review & editing. **Mark Agostini:** Data curation, Resources. **Jay Harvey:** Data curation, Resources. **Rodrigo Zepeda:** Data curation, Resources. **Sasha Alick-Lindstrom:** Data curation, Resources, Writing – review & editing. **Marisara Dieppa:** Data curation, Resources. **Alex Doyle:** Data curation, Resources. **Rohit Das:** Data curation, Resources. **Bradley Lega:** Data curation, Resources. **Kan Ding:** Conceptualization, Data curation, Methodology, Project administration, Resources, Supervision, Investigation, Validation, Visualization, Formal analysis, Writing – review & editing.

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Author Contributions

BZ: manuscript drafting, data collection, analysis, and interpretation; IP: study conceptualization, recruitment, data collection, analysis, and interpretation, manuscript drafting; RH, GP: recruitment, data collection, analysis, and interpretation; MA, JH, RZ, SA; MD, AD, RD, BL: recruitment and data collection; KD: study conceptualization, recruitment, data collection, analysis, and interpretation, manuscript drafting. All authors contributed to revisions of the manuscript and approved the final version.

Conflict of Interest

None of the authors has any conflict of interest to disclose.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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