A novel threshold criterion in transcranial motor evoked potentials during surgery for gliomas close to the motor pathway

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OBJECTIVE Warning criteria for monitoring of motor evoked potentials (MEP) after direct cortical stimulation during surgery for supratentorial tumors have been well described. However, little is known about the value of MEP after transcranial electrical stimulation (TES) in predicting postoperative motor deficit when monitoring threshold level. The authors aimed to evaluate the feasibility and value of this method in glioma surgery by using a new approach for interpreting changes in threshold level involving contra- and ipsilateral MEP.

METHODS Between November 2013 and December 2014, 93 patients underwent TES-MEP monitoring during resection of gliomas located close to central motor pathways but not involving the primary motor cortex. The MEP were elicited by transcranial repetitive anodal train stimulation. Bilateral MEP were continuously evaluated to assess percentage increase of threshold level (minimum voltage needed to evoke a stable motor response from each of the muscles being monitored) from the baseline set before dural opening. An increase in threshold level on the contralateral side (facial, arm, or leg muscles contralateral to the affected hemisphere) of more than 20% beyond the percentage increase on the ipsilateral side (facial, arm, or leg muscles ipsilateral to the affected hemisphere) was considered a significant alteration. Recorded alterations were subsequently correlated with postoperative neurological deterioration and MRI findings.

RESULTS TES-MEP could be elicited in all patients, including those with recurrent glioma (31 patients) and preoperative paresis (20 patients). Five of 73 patients without preoperative paresis showed a significant increase in threshold level, and all of them developed new paresis postoperatively (transient in 4 patients and permanent in 1 patient). Eight of 20 patients with preoperative paresis showed a significant increase in threshold level, and all of them developed postoperative neurological deterioration (transient in 4 patients and permanent in 4 patients). In 80 patients no significant change in threshold level was detected, and none of them showed postoperative neurological deterioration. The specificity and sensitivity in this series were estimated at 100%. Postoperative MRI revealed gross-total tumor resection in 56 of 82 patients (68%) in whom complete tumor resection was attainable; territorial ischemia was detected in 4 patients.

CONCLUSIONS The novel threshold criterion has made TES-MEP a useful method for predicting postoperative motor deficit in patients who undergo glioma surgery, and has been feasible in patients with preoperative paresis as well as in patients with recurrent glioma. Including contra- and ipsilateral changes in threshold level has led to a high sensitivity and specificity.

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KEY WORDS intraoperative monitoring; glioma surgery; motor evoked potentials; motor pathways; threshold level; diagnostic and operative techniques

SURGICAL removal of gliomas is a part of multidisciplinary treatment. Maximal resection should be achieved when feasible, with no or minimal neurological deficit to allow patients to have a reasonable quality of life after the procedure.^{15,22} Unlike cerebral metastases, supratentorial gliomas, especially low-grade ones, are not

well defined, and complete tumor resection can be challenging. In addition to modalities such as diffusion tensor imaging–based functional neuronavigation,²⁸ fluorescence-guided surgery,²⁵ intraoperative ultrasound,^{14,20} and intraoperative MRI,²³ intraoperative monitoring (IOM)^{6,27} has played a significant role in helping neurosurgeons to

ABBREVIATIONS DCS = direct cortical stimulation; IOM = intraoperative monitoring; MEP = motor evoked potentials; TES = transcranial electrical stimulation.

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maximize the extent of tumor resection and to predict postoperative neurological deficits. The IOM techniques have been developed since the 1990s,²⁴ and nowadays there are different approaches for IOM, depending on tumor localization and the function that needs to be evaluated intraoperatively.

Intraoperative monitoring of motor evoked potentials (MEP) to prevent and predict postoperative motor deficit has been well established. MEP can be elicited either through direct cortical stimulation (DCS) or through transcranial electrical stimulation (TES). DCS has been used in most of the studies that have addressed monitoring of MEP during resection of supratentorial lesions in the last 2 decades, and warning criteria such as amplitude reduction (more than 50%) or MEP loss have been well described.^{6,7,9,10,21} However, little is known about the value of MEP after TES in predicting postoperative motor deficit when monitoring threshold level. This method was first presented by Calancie and colleagues for IOM during spinal surgery.²⁻⁴ Later, monitoring of threshold level was used during surgery for cranial lesions, together with the amplitude criterion under DCS or TES in some studies, in which different warning criteria were used and significant numbers of false-negative and false-positive results were reported.^{8,11,16,18,26}

We aimed to evaluate the feasibility and value of the threshold criterion in glioma surgery by using a new approach for interpreting changes in threshold level involving the contra- and ipsilateral MEP.

Methods

Patient Population

Between November 2013 and December 2014, IOM was performed in 103 patients during surgery for supratentorial glioma in motor-eloquent brain areas. In 93 patients the tumor was close to the corticospinal tract, without involving the primary motor cortex (Fig. 1). Therefore, TES was performed to elicit MEP in these patients, because the approach needed did not require craniotomy over the precentral gyrus.

In 10 patients the tumor involved the precentral gyrus, and DCS was used to elicit MEP. The results from DCS in these patients are beyond the scope of this study and will not be reported here.

Clinical Data

All patients underwent clinical examination preoperatively, 24 hours after surgery, at discharge, and after 3 months to assess motor deficits contralateral to the tumor, according to the British Medical Research Council (MRC) grading system (0, no contraction; 1, flicker/trace contraction; 2, active movement with gravity eliminated; 3, active movement against gravity; 4, active movement against resistance; and 5, normal muscle strength). The postoperative neurological motor deficit or deterioration was considered transient if it disappeared during the hospital stay and permanent if it lasted until the follow-up visit, 3 months later.

Preoperative MRI was performed to assess tumor localization. Only patients with tumors close to the motor

FIG. 1. Magnetic resonance images showing examples of gliomas close to the motor pathway. Newly diagnosed glioma in the postcentral gyrus (**A**), newly diagnosed glioma in the insula (**B**), and recurrent glioma within the corticospinal tract (**C and D**).

pathway, who were considered to be at risk for developing postoperative neurological deficit, were included in this study. Contrast-enhancing gliomas were considered eligible for complete resection, unless they were multifocal or with deep infiltration of corpus callosum. Nonenhancing gliomas were considered eligible for complete resection if they did not infiltrate more than one lobe and did not infiltrate the basal ganglia. Postoperative MRI was performed within 48 hours after the procedure to assess the extent of tumor resection and detect postoperative complications such as hemorrhage or territorial ischemia. One patient had a pacemaker, which was not compatible with MRI, and therefore he underwent pre- and postoperative CT scans.

Anesthesia

All procedures were performed after induction of intravenous anesthesia according to a uniform protocol. Muscle relaxants (rocuronium bromide) were applied only for intubation, not during surgery. Anesthesia was induced by propofol, with a target-controlled infusion of 8 µg/ml and continued with 3–4 µg/ml using an infusion pump with a target-controlled infusion function (Perfusor Space, B. Braun), allowing for a constant target blood concentration of propofol during surgery. Analgesia was applied by sufentanil for the intubation and continued with remifentanyl (0.3–0.5 µg/kg/min). Invasive measurement of blood pressure was started prior to the anesthesia induction and stable blood pressure as well as body temperature was

maintained during all procedures. Halogenated anesthetics and nitrous oxide were not used.

Technical Data and Warning Criterion

All procedures were performed after the patients were placed supine, with a physiological head rotation if required. For the TES in the study group, corkscrew-like electrodes were placed subcutaneously at C1, C2, C3, C4, and Cz according to the International 10–20 electroencephalography system. In all cases we performed a bilateral stimulation; C4 to Cz (anode-cathode) stimulation for the right hemisphere and C3 to Cz (anode-cathode) for the left hemisphere. A C2 to C1 (anode-cathode) stimulation or C1 to C2 (anode-cathode) stimulation was performed if the tumor was located adjacent to the falx cerebri and monitoring of the leg muscles was mandatory.

To record MEP, subdermal needle electrodes were inserted bilaterally into the abductor pollicis brevis and tibialis anterior muscles. Additional electrodes were inserted bilaterally into the orbicularis oris muscle when the lesion was lateral enough to put facial function at risk during the surgical procedure. The Endeavor system (Natus Europe GmbH, previously CareFusion) was used for both stimulation and recording of MEP.

The MEP were elicited by transcranial repetitive anodal 5-train stimulation. Threshold level was defined as the minimum voltage needed to evoke a stable motor response from each of the muscles being monitored. Bilateral MEP were continuously evaluated to assess percentage increase in threshold level from the baseline set before dural opening. An increase in threshold level on the contralateral side (facial, arm, or leg muscles contralateral to the affected hemisphere) of more than 20% beyond the percentage increase on the ipsilateral side (facial, arm, or leg muscles ipsilateral to the affected hemisphere) was considered a warning signal.

The MEP monitoring was performed and evaluated by a medical technologist experienced in the field of IOM, who was blinded to the pre- and postoperative neurological function. The decision how to react to the reported changes in MEP was made by the neurosurgeon.

Intraoperative ultrasound was used to localize noneloquent tumor parts (the first to be resected). If the warning signal took place, the tumor resection was halted to apply warm irrigation and repositioning of the fixed and dynamic retraction of brain tissue to exclude its influence on

MEP. Afterward, if the threshold level recovered, tumor resection was continued. In case of a persistent increase in threshold level of more than 20% on the contralateral side, beyond the percentage increase on the ipsilateral side, tumor resection was terminated. Recorded alterations were subsequently correlated with postoperative neurological deterioration and MRI findings.

Informed consent was obtained from all patients prior to the surgical procedure. The data were collected prospectively according to the local ethical standards. For all tests, a *p* value less than 0.05 was considered significant. Statistical analysis and graphics were performed using Microsoft Excel (2013, Microsoft Inc.) and SigmaPlot (v12.5, Systat Software Inc.).

Results

Transcranial electrical stimulation was successfully performed during glioma surgery in 93 patients between November 2013 and December 2014. The mean age of the patients was 56 years (range 25–81 years). No major complications related to TES were reported—especially no seizures. Tumor grading and localization are presented in Table 1. No changes in MEP were observed during patient positioning; all significant changes in threshold level took place during tumor resection.

Intraoperative Changes in Threshold Level and Clinical Outcome

In 73 of 93 (78.5%) patients preoperative paresis was not present. The starting values for threshold level in these patients ranged from 88 to 324 V, with a median of 118 V. In 5 of those patients, a significant change in threshold level was observed and did not recover at the end of the procedure, and all 5 showed new paresis postoperatively (transient in 4 patients and permanent in 1).

Preoperative paresis was detected in 20 of 93 patients (21.5%). The starting values for threshold level in these patients ranged from 60 to 296 V, with a median of 126 V. In 8 of those patients, a significant change in threshold level was observed and did not recover at the end of the procedure, and all 8 showed postoperative neurological deterioration (transient in 4 patients and permanent in 4).

In 80 of 93 patients (86%), no significant change in threshold level was detected, and none of these patients showed postoperative neurological deterioration. Table 2

TABLE 1. Tumor grade and localization in 93 patients with gliomas close to the motor pathway

Location	WHO Classification of CNS Tumors*							
	Glioblastoma, IV	Astrocytoma		Oligodendroglioma		Oligoastrocytoma		Others
		III	II	III	II	III	II	
Frontal	22	8	3	1	3	4	0	1 PA
Parietal	12	0	1	0	0	1	0	1 PX
Temporal	17	2	0	2	0	0	0	1 PX
Insular	6	3	0	2	1	1	1	0
Total	57	13	4	5	4	6	1	3

PA = pilocytic astrocytoma; PX = pleomorphic xanthoastrocytoma.

* Graded according to Louis DN, Ohgaki H, Wiestler OD, et al (eds): *WHO Classification of Tumours of the Central Nervous System*. Lyon, France: IARC Press, 2007.

TABLE 2. Demographic and clinical data in 13 patients with significant changes in threshold level

Case No.	Age (yrs)	Tumor Localization	Tumor Status, WHO Grade*	Threshold Level in Contralat Muscles			Threshold Level in Ipsilat Muscles			Difference†	Preop Muscle Strength‡	Postop Muscle Strength‡			Tumor Resection
				Starting Value (V)	Final Value (V)	Percentage Change	Starting Value (V)	Final Value (V)	Percentage Change			After 24 Hrs	At Discharge	After 3 Mos	
1	70	Insula	New, IV	168	212	26%	340	340	0%	26%	4	2	4	4	GTR
2	75	Temporal lobe	New, IV	92	120	30%	88	92	5%	25%	5	3	5	5	STR 1
3	55	Insula	Rec, IV	128	188	47%	112	104	-7%	54%	5	2	3	3	GTR
4	41	Frontal lobe	New, IV	116	140	21%	148	140	-5%	26%	4	2	4	4	STR 1
5	77	Frontal lobe	New, IV	152	244	61%	144	148	3%	58%	4	2	3	3	GTR
6	78	Temporal lobe	New, IV	80	108	35%	96	104	8%	27%	5	3	5	5	GTR
7	51	Parietal lobe	New, IV	144	168	17%	224	196	-13%	29%	5	3	5	5	GTR
8	81	Parietal lobe	Rec, IV	296	400	35%	100	108	8%	27%	4	2	4	4	GTR
9	55	Insula	New, IV	208	400	92%	296	400	35%	57%	3	1	1	1	STR 2
10	48	Frontal lobe	New, IV	96	128	33%	0	0	0%	33%	5	3	5	5	GTR
11	42	Frontal lobe	Rec, III	232	272	17%	108	100	-7%	25%	4	2	4	4	GTR
12	77	Parietal lobe	New, II	124	224	81%	92	104	13%	68%	4	2	3	3	GTR
13	25	Insula	New, IV	120	250	108%	120	145	21%	88%	4	1	3	3	STR 2

GTR = gross-total resection; rec = recurrent; STR 1 = subtotal resection without nodular enhancement; STR 2 = STR with nodular enhancement.

* Graded according to Louis DN, Ohgaki H, Wiestler OD, et al (eds): *WHO Classification of Tumours of the Central Nervous System*. Lyon, France: IARC Press, 2007.

† Percentage change in threshold level in the contralateral muscles minus percentage change in threshold level in the ipsilateral muscles.

‡ British Medical Research Council grading system: 0, no contraction; 1, flicker/trace contraction; 2, active movement with gravity eliminated; 3, active movement against gravity; 4, active movement against resistance; 5, normal muscle strength.

shows the significant changes in threshold level, with the outcome for motor function. Figure 2 demonstrates examples of bilateral MEP monitoring in 4 patients with different changes in threshold level.

In 62 of 93 cases (66.7%), patients presented with newly diagnosed glioma, and in 31 of 93 cases (33.3%) they presented with recurrent glioma. The starting values of threshold level ranged in both subgroups between 60 and 324 V, with a median of 116 V in patients with newly diagnosed glioma and a median of 148 V in patients with a recurrent glioma. Of those with newly diagnosed glioma, 10 patients showed a significant persistent change in threshold level, and all of them developed a deterioration of their motor function postoperatively (transient in 6 patients and

permanent in 4). Of those with recurrent glioma, 3 patients showed a significant persistent change in threshold level, and all of them developed a deterioration of their motor function postoperatively (transient in 2 patients and permanent in 1).

In 8 patients (Cases 1, 2, 4, 6, 7, 8, 10, and 11) the increase in the threshold level (beyond the increase on the ipsilateral side) didn't exceed 50%, and those patients developed a transient new paresis or a transient deterioration postoperatively, which recovered during the hospital stay. In 5 patients (Cases 3, 5, 9, 12, and 13) the increase in threshold level was more than 50%, and all of them developed a postoperative permanent motor deficit or motor deterioration (Table 2). In 60 other patients, the threshold

FIG. 2. Examples of bilateral MEP monitoring in 4 patients, recorded from abductor pollicis brevis, demonstrating the percentage changes in threshold level (V) between baseline and closing, and the differences between contra- and ipsilateral sides. In examples 1 and 2, the patients didn't show any postoperative deterioration of motor function; in example 3, the patient developed a transient postoperative motor deficit; and in example 4, the patient developed a permanent postoperative motor deficit.

level increased during the procedure (in 10 of them more than 20%), yet the difference compared with the increase on the ipsilateral side was still less than 20%. None of these patients developed a new motor deficit or deterioration postoperatively. In the remaining 20 patients, no increase in the threshold level was noticed and none of them showed a postoperative motor deficit.

Changes in Threshold-Level and MRI Findings

According to the postoperative MRI scans, gross-total resection was achieved in 56 of 82 patients (68%) in whom complete tumor resection was attainable. Subtotal resection was achieved in 37 patients (40%), in 11 of whom complete resection was not attainable. In 4 patients the tumor resection was stopped due to a persistent significant change in threshold level, and the postoperative MRI showed rim enhancement of the resection cavity in 2 of them and residual nodular enhancement in the other 2. In the remaining 22 patients, no significant changes in threshold level took place, and although parts of the tumor were not very visible either microscopically or using the ultrasound, and the postoperative MRI studies showed rim enhancement of the resection cavity in 12 patients, residual nodular enhancement in 4 patients, and residual low-grade tumor in 6 patients.

Postoperative ischemia adjacent to the resection area was detected in 4 patients; in 2 of them (Cases 2 and 7, Table 2) a significant change in threshold level took place during the procedure and both patients developed a postoperative new motor deficit, which recovered during the hospital stay. The threshold level in the remaining 2 patients did not change significantly and no neurological deterioration appeared postoperatively.

Statistical Analysis

In this series, the sensitivity and positive predictive value were estimated at 100%, with a 95% CI of 75.12%–100%,¹ and the specificity and negative predictive value were estimated at 100%, with a 95% CI of 95.45%–100%.¹

The starting values of threshold levels in patients with preoperative paresis were not significantly higher than in patients without preoperative paresis (median 126 and 118 V, respectively; Mann-Whitney rank-sum test, $p = 0.5$). Nevertheless, there were significantly more patients with preoperative paresis who developed a significant change in threshold level and postoperative neurological deterioration, than there were patients with no preoperative paresis (OR 9, 95% CI 2.53–32.44; $p = 0.0007$).

The starting values of threshold levels in patients with recurrent glioma were significantly higher than in patients with newly diagnosed glioma (median 148 and 116 V, respectively; Mann-Whitney rank-sum test, $p = 0.018$). However, no significant difference was found in the rate of significant changes in threshold level or postoperative motor deficit ($p = 0.4$).

Discussion

Transcranial electrical stimulation is a feasible method for eliciting MEP during surgery for supratentorial glioma, especially when the precentral gyrus is not involved

in the tumor. It enables the surgeon to perform a smaller craniotomy and to avoid subdural positioning of the strip electrode without visual control and mapping of the motor cortex, which is necessary when applying DCS. In our study, TES was performed successfully in 93 patients during surgery for gliomas close to the motor pathway, with 100% sensitivity and specificity. Furthermore, monitoring of the threshold level, defined as the minimum voltage needed to evoke a stable motor response from each of the muscles being monitored, allowed us to reduce patient movement during tumor resection to a minimum.

Previous studies addressed the latency of MEP, and reported that latency changes showed wide variations^{7,10,17} and that latency prolongation resulted in low sensitivity and specificity.¹⁰ Therefore, we didn't use latency changes as a warning criterion in our patient cohort.

According to the literature,^{7,9,10} the definition of the amplitude criterion varies from amplitude decline of more than 50% or 80% to amplitude loss. There is also variability in the stimulus intensity when using the amplitude criterion in intraoperative MEP.¹⁹ In addition, bilateral changes in the threshold level during surgical procedures have been described in previous series,^{12,13,26} and only monitoring of the affected and unaffected hemisphere alike allows the detection of general effects (e.g., anesthesia, hypotension) on cortical excitability and thus the elicibility of MEP.²⁶ However, there is so far no clear algorithm to include the changes of ipsilateral threshold level in the evaluation of the warning criteria.

A Novel Threshold Criterion

In the current study we introduced a novel interpretation of the threshold criterion involving bilateral threshold levels, which enabled us to incorporate all changes of threshold level caused by general anesthesia, brain shift, and pneumocephalus, and to achieve a high level of sensitivity and specificity.

The threshold criterion was first introduced in 1998,³ in a study in which an increase in the threshold level of more than 100 V during at least 1 hour was found to be predictive for postoperative neurological deficit, without false-negative or false-positive results, in a series of 34 patients who underwent spinal surgery. A further study in 2001 by Calancie et al., which evaluated the threshold criterion during spinal surgery in 194 patients, was able to confirm the predictive value of this criterion during spinal surgery.² In the last decade, this criterion has been used in cranial surgery (Table 3) in combination with the amplitude criterion, but its value in predicting postoperative neurological deficit in glioma surgery has not been ultimately clarified,¹⁹ taking into consideration the technical and pathophysiological differences between spinal and cranial surgeries. Krammer et al. used the combination of amplitude criterion and threshold criterion.⁸ They defined the latter as an increase in threshold level of more than 20% compared to the baseline. However, changes in the ipsilateral threshold level were not considered, which might have been responsible for the false-positive results in their series.

Transient and Permanent Motor Deficit

In our cohort, 8 patients showed an increase in thresh-

TABLE 3. Literature review of glioma series that applied TES

Authors & Year	No. of Patients	Stimulation Method	Warning Criteria	True Negative	False Negative	True Positive	False Positive
Neuloh et al., 2007 ¹⁶	72	TES/DCS	Amplitude*	38	2	20	12
Neuloh & Schramm, 2004	88	TES/DCS	Amplitude*	45	2	29	12
Krammer et al., 2009	62	TES	Amplitude,* threshold level†	33	0	9	20
Szelényi et al., 2010	29	TES	Amplitude,* threshold level‡	NA	NA	13	16
Lee et al., 2014	84	TES	Amplitude*	66	11	3	4
Present study	93	TES	Threshold level§	80	0	13	0

NA = not available.

* Amplitude decline or loss.

† Increase in threshold level > 20%.

‡ Increment of threshold > 20 mA or > 100 V.

§ Increase in threshold level > 20% beyond the increase on the ipsilateral side.

old level of 20%–50% beyond the change on the ipsilateral side, and 5 patients showed an increase in threshold level of more than 50% beyond the change on the ipsilateral side. All 13 of these patients suffered a new postoperative motor deficit/deterioration, but it was transient in the first subgroup (8 patients) and permanent in the second (5 patients). We propose that an increase in threshold level of more than 50% beyond the ipsilateral change is likely to predict a permanent motor deficit/deterioration, although we could not confirm it yet due to the relatively small number of patients with a permanent postoperative motor deficit/deterioration.

Preoperative Paresis

When using the amplitude criterion, preoperative paresis reduces the feasibility of DCS-MEP.⁵ In our study, 21.5% of the patients suffered from preoperative paresis. TES was applied successfully in all of them, and the initial values of threshold level were not significantly higher than in patients with no preoperative paresis. More patients with preoperative paresis showed significant changes in threshold level and, accordingly, postoperative motor deterioration.

Recurrent Glioma

Of our patient cohort, 33.3% harbored recurrent gliomas. Although the initial values of threshold level in these patients were significantly higher than in those with a newly diagnosed glioma, MEP could be elicited in all of them. Also, there was no difference in the rate of significant changes in threshold level or postoperative paresis compared to the remaining patients.

Limitations and Areas of Further Research

The limitation of our threshold criterion is the need for bilateral transcranial MEP, which is hardly possible when the tumor involves the primary motor cortex and the craniotomy has to expose this area. Further investigations will be necessary to compare the new threshold criterion with the amplitude criterion, to define the cutoff for permanent paresis, and to evaluate its usefulness during vascular surgery.

Conclusions

Monitoring of threshold level using the novel threshold criterion after TES is a safe and reliable method for predicting postoperative motor deficit during surgery for gliomas located close to the motor pathway. Involving bilateral threshold levels in the evaluation of the MEP has led to high specificity and sensitivity. This method seems to be feasible in patients with preoperative paresis as well as in patients with recurrent glioma.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Supplemental Information

Previous Presentations

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Author Contributions

Conception and design: Abboud. Acquisition of data: Abboud, Schaper, Dührsen, Schwarz. Analysis and interpretation of data: Abboud. Drafting the article: Abboud. Critically revising the article: Schmidt, Westphal, Martens. Approved the final version of the manuscript on behalf of all authors: Abboud. Statistical analysis: Abboud. Administrative/technical/material support: Schwarz. Study supervision: Abboud, Martens.

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