



The Potential of S100 Calcium-Binding Protein B and Glial Fibrillary Acid Protein in Predicting the Intracranial Lesions in Mild Traumatic Brain Injury: A Systematic Review of Literature

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Abstract

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AIM: To summarize the current evidence of S100 calcium-binding protein b (S100B) and glial fibrillary acid protein (GFAP) in predicting intracranial lesions after mild traumatic brain injury (mTBI).

MATERIALS AND METHODS: We searched publications on biomarkers in mTBI from Web of Science, PubMed, and Scopus between January 1990 and July 2021. We included randomized controlled trials (RCTs), cohort, case control, and cross-sectional studies that involved patients with acute closed mTBI in all age group in which head computed tomography (CT) scan and blood-based biomarkers (GFAP and S100B) examination were conducted under 24 h. This study was registered in Open Science Framework.

RESULTS: The initial search identified 4.937 article, in which 127 were included for full-text assessment. A total of 16 articles were finally included. No RCT was found in literature searching. Thirteen studies were studying S100B and three studies were studying GFAP. Nine out of 13 S100B studies shows a promising result with $\geq 95\%$ sensitivity for detecting intracranial lesions. Majorities (11/13) studies of S100B confirmed that S100B reduced the unnecessary usage of CT scan. GFAP concentration significantly increased in CT+ patient than CT- patient. No specific GFAP cutoff value between the studies was found.

CONCLUSION: The result showed that S100B and GFAP had potential to predict the occurrence of intracranial lesions. Variance between methodologies and cutoff value hindered the quality of evidence, especially in GFAP.

Introduction

The majority (80%–90%) of traumatic brain injury is mild traumatic brain injury (mTBI) [1]. MTBI can be accompanied by intracranial lesions and may lead to a bad prognosis for the patient if not diagnosed properly [2]. Computed tomography (CT) scan is the gold standard for diagnosing mTBI in the emergency department [3]. However, the lack of objective clinical signs in determining the intracranial lesions in mTBI may lead to overdiagnosing and increase the number of unneeded CT scan. The frequent use of CT scans can be an economic burden to the hospital and the usage of CT scans may carry an iatrogenic risk [4], [5], [6]. A study states that a 10% decrease in the amount of CT scans used in MTBI patients could save over \$20 million each year [7]. While one study shows only 36% of CT scans accurately diagnose intracranial lesions in mTBI, shows the need to increase the effectiveness of CT scans in diagnosing mTBI.

CT scan carries significant iatrogenic risk. A single head CT raises the chance of eventual cancer

by a factor of two, with repeated CTs giving cumulative susceptibility [5], [6]. Many research suggests that several blood-based brain injury biomarkers may help identify which individuals may have acute intracranial lesions, thus lowering the usage of unneeded head CT scanning. Blood test is much easier to obtain and fit with the characteristics of the emergency department. Both S100 calcium-binding protein b (S100B) and glial fibrillary acid protein (GFAP) were studied and shows promising results in predicting intracranial lesions [7], [8] and may be used as an objective sign to determine whether CT scan is needed or not.

Following mTBI, axonal shearing and cellular damage induces neuronal and astrocyte biomarker release [9], [10]. Neurons biomarker are NF-L, UCH-L1, and tau, whereas astrocytes produce GFAP and S100B [9]. These biomarkers are discharged into the interstitial fluid around them. The blood-brain barrier may also be disrupted following mTBI. These disruption can cause S100B and GFAP to spread into extracellular space of the brain and permeate to blood vessels [11]. It has been studied that transitory disruption of the blood brain barrier occurs in roughly

50% of mTBI cases [12]. Additional pathways that is likely to account for S100B and GFAP entry into the blood following mTBI are CSF is redistributed to the blood via venous drainage and circulation through the glymphatic system [13]. However, the specific process which biomarkers escape the interstitial fluid and leak into the lymph system before returning to the blood remain unknown [14].

Several studies on S100B pointed the potential to S100B screening test to reduce unnecessary CT scan. S100B has also been implemented in Scandinavian guidelines for initial management of minimal, mild, and moderate head injuries since 2013. An increase in GFAP serum related with acute brain pathology as indicated by head CT [15], [16]. Increases in serum levels can be seen within hours of damage and can last for days, providing biomarker profile which makes GFAP detection potentially very helpful and practical in an emergency situation [17].

Thus, the goal of this comprehensive study is to compile the effectiveness of both S100B and GFAP for diagnosing intracranial lesions and as well as to try to compare which biomarker is more useful for diagnosing intracranial lesions in mTBI.

Methods

Search strategy

Preferred reporting items for systematic reviews and meta-analyses (PRISMA) were adopted to formulated this study [18]. Databases that were used to search relevant articles were PubMed, World of Science, and Scopus with time limitation between January 1990 and July 2021. The search was restricted to articles written in English. The search formula were: (Mild head trauma OR Mild brain injur* OR Mild brain trauma OR MTBI OR Minimal head injur* OR Minimal head trauma OR Minimal brain injur* OR Minimal brain trauma OR Concussion) AND (Intracranial lesion* OR Intracranial abnormali* OR Intracerebral hemorrhage OR traumatic OR Hematoma, subdural, acute, OR Subdural hematoma OR Hematoma, epidural, cranial OR Epidural hematoma OR Cerebral hemorrhage, traumatic OR Subarachnoid hemorrhage OR Diffuse axonal injur*.) AND (S100B OR Serum S100B OR S100 Calcium-binding protein beta subunit OR S-100B OR Serum S-100B OR S-100 Calcium-binding protein beta subunit OR NTP-S-100beta OR NTP S 100beta OR Glial fibrillary acidic protein* OR Astroprotein OR Glial fibrillary acid protein OR Glial intermediate filament protein OR GFA-protein OR GFAP OR GFAP-BDP). We also limited our research to cohort studies, cross-sectional studies, and randomized controlled trials (RCTs).

Inclusion and exclusion criteria

The inclusion criteria are as follows: (1) Patients diagnosed with mTBI <24 h, (2) Measurement of blood biomarkers in the first 24 h after mTBI, 3. CT scan and magnetic resonance imaging were used to diagnose intracranial lesions within 24 h after trauma. We excluded the literature with penetrating head trauma, intracranial abnormalities, or diseases, only studied cerebrospinal biomarkers, and another systematic review or meta-analysis.

Quality assessment and data extraction

Journal quality assessment will be carried out independently by two reviewers to minimize bias. All cross-sectional studies, case-control studies, and cohort studies that have been collected will be assessed for journal quality using the Newcastle Ottawa Scale (NOS) [19]. Articles of cross-sectional studies, case-control studies, and cohort studies that will be included in this study must have a total score of 7 or more on the NOS criteria. The RCT journal quality assessment will be conducted using the Cochrane Risk of Bias 2 Tool [20]. The difference between journal quality scoring will be discussed between two reviewers to reconcile the mismatch. Data collection was performed independently and differences in data collection will be resolved by discussion between 2 reviewers. The collected data were (1) author, (2) years, (3) type of study, (4) number of patients, (5) patient age, (6) patient Glasgow Coma Scale (GCS), (7) type of biomarker studied, (8) type of sample (serum or plasma), (9) biomarker specification, (10) biomarker concentrations, and (11) sampling time.

Results

Study selection and characteristic

Figure 1 depicts the PRISMA flow chart of this study. During the initial search, 4937 items were discovered. After applying all of the inclusion and exclusion criteria, fourteen manuscripts remained in the final pool. Table 1 shows a summary of the studies that were included.

This systematic review included thirteen cohort studies and one cross-sectional study. No randomized control studies were identified. A pediatric sample was used in four studies [21], [22], [23], [24], and a sample older than 16 years was used in ten studies [25], [26], [27], [28], [29], [30], [31], [32], [33], [34]. A skier was utilized as a test subject in one research.

S100B was studied in the majority of studies, with total of 13 of the 14 studies [21], [22], [23], [24],

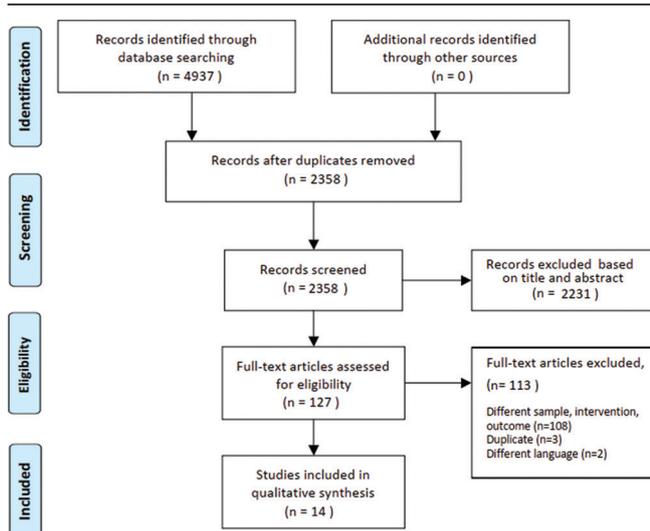


Figure 1: Preferred reporting items for systematic reviews and meta-analyses flow chart

[25], [26], [27], [28], [29], [30], [31], [32], [33], whereas the GFAP biomarker was discussed in 3 studies [26], [29], [34]. Two studies studied both S100B and GFAP biomarker. The most commonly utilized specimen was serum, which was used in 12 of the 14 studies.

Patient demographic

A total of 3,424 participants in S100B studies and 924 participants in GFAP studies were enrolled in this review. The sample size varies from 40 to 1309 in S100B studies and 176 to 566 in GFAP studies. Pediatric sample accounts 13.2% (258) of total sample. Domestic and traffic-related accidents are the most common cause of mTBI in the sample. In total, 2975 (87%) patients were classified with GCS 15 and 449 (13%) patients had GCS score 13 or 14. The mean age of the sample cannot be classified due to difference in measures of central tendency.

Risk of bias

All of the studies were yielded a good quality from the evaluation. Table 2 shows the findings of the Newcastle–Ottawa Scale. The average ratings for the 14 studies on the Newcastle–Ottawa Scale were as follows: selection (0–4) = 3.07; comparability (0–2) = 2.00; and outcome (0–3) = 2.23.

Discussion

Finding in S100 calcium-binding protein b studies

The S100B biomarker is the most studied biomarker with a total of 13 articles discussing the

S100B biomarker. Based on the results of this study, the S100B biomarker has high sensitivity with low specificity. It is indicated that 9 of 13 articles showed the sensitivity of S100B in predicting the occurrence of intracranial lesions more than equal to 95% and 9 of 13 articles showed the specificity of S100B in predicting the occurrence of intracranial lesions of less than 50%.

The cut-off value used in the S100B examination has started to have a determined value compared to GFAP. The cutoff value of 0.10 g/L was used in 6 of the 13 articles and 0.105 g/L was used in 2 of the 13 articles.

A total of 11 out of 11 articles that examined the relationship between serum concentrations of S100B in the CT scan negative group with CT scan positive showed a close relationship and indicated that the S100B examination has the potential to diagnose intracranial lesions in patients with mTBI. There were relationship between age and serum S100B levels in the age group <65 years (n = 129) and 65 years (n = 43) and found that S100B levels at the age of 65 years were higher than <65 years (30). year with $p = 0.004$. According to Kelmendi *et al.*, 2018 there was an increase in S100B levels with increasing age in pediatric samples, but the difference was not significant ($p = 0.084$).

A total of 11 of 13 articles concluded that early examination of the S100B could reduce the use of unnecessary CT scans to diagnose intracranial lesions in cases of mTBI. There is one study [25] that opposed the correlation between S100B and intracranial hemorrhage and declare that it would miss many clinically important brain injuries in non-hospitalized patients. Another study [27] stated that the utility of S100B may vary depending on several confounding factors, such as exercise training and fractures. For minor ski-related head injuries, the S100B did not show any significant reduction in the use of CT scans.

Finding in glial fibrillary acid protein study

Two study [29], [34] found that the mean serum GFAP on CT+ was higher than on CT- and there was a significant increase in serum GFAP levels on CT+ compared to CT-. There is also an agreement between the conclusions in these two studies. Lewis *et al.*, 2017 concluded that GFAP examination within 6 h after a head injury may be useful in identifying and stratifying brain injury severity in emergency department patients with head trauma, but is not reliable for ruling out the diagnosis of concussion. However, positive GFAP is associated with the presence of a concussion. Forouzan *et al.*, 2021 concluded that the diagnostic ability of GFAP for intracranial lesions is still lacking, but GFAP, as a predictive factor in persons with a diagnosis of mTBI requiring neurologic surgery, shows a favorable diagnostic effect.

Table 1: Summary of S100B and glial fibrillary acid protein findings

Author	Study design	Sample size (n)	Sample age (years)	GCS (n)	Biomarker type	Sample type	Sample analysis	Biomarker specification	Biomarker concentration	Sampling time
Seidenfaden et al., 2021	Prospective observational multicenter cohort study	566 CT+ (32) CT- (534)	Median (IQR): 62 (45–74)	15 (453) 14 (113)	S100B	Serum	Cobas® e602 analyzer	Cut off value 0.10 µg/L Sensitivity 100% Specificity 15.4% NPV 100%	Mean Prähospital: 0.29 µg/L Inhospital: 0.17 µg/L	Median Prähospital 45 min (IQR: 27–84) Inhospital 108 min (IQR: 85–149) <6 h
Blais Lécuyer et al., 2021	Prospective multicentre cohort study	320	< 65 (421) ≥ 65 (65)	15 (408) 14 (63) 13 (6)	S100B	Plasma	ELISA	NPV 6.6% Cut off value: 0.10 µg/L Sensitivity 18.2% Specificity 88.5%	Median (IQR) CT+: 0.043 µg/l (0.008–0.080) CT-: 0.039 µg/l (0.023–0.059)	< 3 h
Kahouadji et al., 2020	Prospective cohort study	130 CT- (97) CT+ (33)	Mean ± SD: 44.8 ± 20.4	15 (108) 13–14 (22)	S100B	Serum	Roche Diagnostics Cobas e411	Sensitivity 97% (95% CI: 84.2–99.9) Specificity 11% (95% CI: 5.8–19.4) PPV 27% NPV 92%	CT+: 0.18 µg/L (minimum: 0.05; maximum: 1.21; IQR: 0.13–0.28) CT-: 0.31 µg/L (minimum: 0.08; maximum: 1.2; IQR: 0.17–0.62)	Mean CT+: 2.79 h CT-: 2.66 h
Mozafari et al., 2019	Cross sectional study	40 CT- (20) CT+ (20)	Median (range) CT-: 6.6 (0.5–18) CT+: 9 (2–18)	15 (23) 14 (17)	S100B	Serum	ELISA	Cut off value 0.1725 µg/L Sensitivity 95% Specificity 100% PPV 100% NPV 91%	Mean ± SD CT+: 561 ± 283 ng/L CT-: 79.8 ± 22.8 ng/L	Mean CT+: 2.79 h CT-: 2.66 h
Kelmendi et al., 2018	Single-center prospective cohort study	80 CT+ (53) CT- (27)	Mean ± SD: 9.1 ± 3.8	15 (25) 14 (26) 13 (27)	S100B	Serum	Elecsys	Cut off value: 0.105 µg/L Sensitivity 100% Specificity 26.56%	Mean ± SD All sample: 0.398 µg/L (± 0.298 µg/L) <5 years: 0.308 µg/L (± 0.254 µg/L) 5–9 years: 0.338 µg/L (± 0.253 µg/L) >10 years: 0.476 µg/L (± 0.329 µg/L)	< 3 h
David et al., 2017	Prospective, observational study	308 CT- (275) CT+ (33)	Mean ± SD Total: 79.1 ± 10.5 CT-: 79.2 ± 10.2 CT+: 78.0 ± 12.8	15 (800) 13–14 (8)	S100B	Serum	Elektrochemiluminescence immunoassay on the Roche cobas e602 instrument	Cut off value 0.105 µg/L Sensitivity 84.8% (95% CI: 68.1–94.9) Specificity 30.2% (95% CI: 24.8–36.0) NPV 94.3% (95% CI: 87.2–98.1%) PPV 12.7% (95% CI: 8.6–17.9%)	Median CT-: 120.0 pg/mL (75.0–240.0) CT+: 225.0 pg/mL (165.0–375.0)	Mean: 214.5 ± 113.3 min
Lewis et al., 2017	Prospective, multicenter, observational clinical trial	172 CT- (140) CT+ (32)	Mean ± SD CT-: 42.9 ± 17.4 CT+: 53.0 ± 17.7	15 (168) 14 (15) 13 (6)	S100B	Serum	ELISA	Cut off value ≥ 35 pg/ml Sensitivity 96.5% (92.6–98.7) Specificity 5.3% (1.1–14.6) PPV 75.5% NPV 33.3%	Median CT-: 120.0 pg/mL (75.0–240.0) CT+: 225.0 pg/mL (165.0–375.0)	<6 h after trauma
Lagerstedt et al., 2017	Prospective cohort study	172 CT+ (32) CT- (140)	Mean ± SD CT-: 46 ± 20 CT+: 61 ± 25	15 (172)	S100B	Serum	EZHHS100B-33K and Elecsys	Sensitivity 81% Specificity 42% NPV 25.2% PPV 92.6%	N/A	N/A Mean: 198 min CT-: 199 ± 86 min CT+: 194 ± 96 min
Manzano et al., 2016	Prospective cohort study	73 CT+ (20) CT- (53)	Mean ± SD CT-: 7.83 ± 4.71 CT+: 6.51 ± 3.7	13–15 (73)	S100B	Serum	Elecsys	Cut off value: 0.14 µg/L 2 years Sensitivity 50.0% (5%–97%) Specificity 14.3% (1%–28%) 2–16 years Sensitivity 100.0% (81%–100%) Specificity 37.0% (30%–37%) All sample: Sensitivity 95.0% (77%–100%) Specificity 34.0% (27%–36%)	Mean ± SD CT-: 0.35 µg/l (± 0.45) CT+: 0.97 µg/l (± 1.29) 2 years: 0.40 µg/l (± 0.35) 2–16 years: 0.54 µg/l (± 0.86) All sample: 0.52 µg/l (± 0.81)	CT-: 163.8 min (84.7) CT+: 186.0 min (106.0)
Bouvier et al., 2012	Prospective cohort study	65 CT- (42) CT+ (23)	< 16 (65)	13–15 (65)	S100B	Serum	n electrochemiluminescence immunoassay on a Roche Diagnostics Modular Analytics system E170 instrument	Cut off value: 0.18 µg/L Sensitivity 100% (85.2%–100%) Specificity 33% (20%–50%) PPV 45% (31%–60%) NPV 100% (77%–100%)	Median CT-: 0.57 µg/L (IQR 0.29–0.90) CT-: 0.28 µg/L (range 0.14–0.41)	2 h 05 min (range 1 h 30 min - 2 h 45 min)
Bberthaler et al., 2006	Prospective cohort study	1309 CT- (1216) CT+ (93)	Median 47 (32–65)	13 (65) 14 (122) 15 (1152)	S100B	Serum	Elecsys S100	Cut off value 0.1 µg/L Sensitivity 99% (95% CI: 96%–100%) Specificity 30% (95% CI: 29%–31%)	Median (IQR) CT-: 0.16 µg/L (0.09–0.33 µg/L) CT+: 0.49 µg/L (0.25–1.46 µg/L)	Median 60 min (range, 40–80)

(Contd...)

Table 1: (Continued)

Author	Study design	Sample size (n)	Sample age (years)	GCS (n)	Biomarker	Sample type	Sample analysis	Biomarker specification	Biomarker concentration	Sampling time
Poli-de-Figueiredo et al., 2006	Prospective cohort study	50 CT+ (6) CT- (44)	> 18	15 (37) 14 (11) 13 (2)	S100B	Serum	Elecsys	Cut off value 0.1 µg/L Sensitivity 100% Specificity 20% NPV 100% PPV 15%	Median all sample (IQR): 0.29 µg/L (0.14–0.76 µg/L) CT+: 0.75 µg/L (0.62–6.5 µg/L) CT-: 0.26 µg/L (0.12–0.65 µg/L)	Median (IQR): 82 min (60–110 min)
Mussack et al., 2002	Prospective cohort study	139 CT- (120) CT+ (19)	Median: 36 CT+: 56.2 (33.8–67.9) CT-: 34.2 (26.9–58.5)	13–14 (10) 15 (129)	S100B	Plasma	LIAISON Sangtec100	Cut off values > 0.21 µg/L Sensitivity 100% Specificity 50.0% PPV 24.1% NPV 100%	Median CT+: 0.94 (0.39–1.43) ng/mL CT-: 0.22 (0.14–0.39) ng/mL	N/A
Seidenfaden et al., 2021	Prospective observational multicenter cohort study	566 CT+ (32) CT- (534)	Mean: 62 (45–74)	15 (453) 14 (113)	GFAP	Serum	ELISA	Cut off value ≥ 0.045 ng/mL Sensitivity 6.3% Specificity 99.3% NPV 94.6%	Mean Pra hospital: 0.29 ng/mL Inhospital: 0.17 ng/mL	Median Pra hospital: 45 min (IQR: 27–84) Inhospital: 108 min (IQR: 65–149) Abnormal CT scan: 0.81 ± 0.25 h Normal CT scan: 0.84 ± 0.23 h < 6 h
Forouzan et al., 2021	Prospective epidemiological analysis	176 CT+ (8) CT- (168)	Mean ± SD Total: 36.4 ± 16 CT+: 64.78 ± 20.3 CT-: 35.04 ± 14.5	13–15 (176)	GFAP	Serum	chemiluminescent immunoassay sandwich	Cut off value 1.35 ng/ml Sensitivity 50% Specificity 44%	Mean total: 2.67 ± 2.12 ng/mL CT+: 4.27 ± 6.17 ng/mL CT-: 2.02 ± 2.37 ng/mL	
Lewis et al., 2017	Secondary analysis of a prospective, multicenter, observational clinical trial	172 CT- (154) CT+ (34)	Mean ± SD CT-: 42.5 ± 17.4 CT+: 53.0 ± 17.7	15 (168) 14 (15) 13 (6)	GFAP	Serum	ELISA	Cut off value ≥ 0.03 ng/mL Sensitivity 44.2% (36.9–51.6), Specificity 94.9% (85.9–98.9) NPV 96.5% PPV 34.8%	GFAP (ng/mL) CT+: 0.1192 (0.03–0.4375) CT-: 0.02 (0.02–0.0367)	

IQR: Interquartile range, GCS: Glasgow coma scale, CT: Computed tomography, NPV: Negative predictive value, PPV: Positive predictive value, SD: Standard deviation, CI: Confidence interval, N/A: Not available, GFAP: Glial fibrillary acid protein, ELISA: Enzym-Linked Immunosorbent Assay.

Table 2: Newcastle Ottawa Scale Score of the Journal

Serial number	Authors	Study design	Selection cohort			Comparability			Outcome			Total
			1	2	3	4	1	2	3			
1	Lecuyer et al. 2021	Cohort	*	*	*	**			*	*	*	8
2	Kelmendi et al. 2018	Cohort	*	*	*	**			*	*	*	7
3	Lagerstedt et al. 2017	Cohort	*	*	*	**			*	*	*	7
4	Manzano et al. 2016	Cohort	*	*	*	**			*	*	*	7
5	Forouzan et al. 2021	Cohort	*	*	*	**			*	*	*	7
6	Poli-de-Figueiredo et al. 2006	Cohort	*	*	*	**			*	*	*	7
7	Seidenfaden et al. 2021	Cohort	*	*	*	**			*	*	*	7
8	Lewis et al. 2017	Cohort	*	*	*	**			*	*	*	7
9	Bouvier et al. 2012	Cohort	*	*	*	**			*	*	*	7
10	Kahouadji et al. 2020	Cohort	*	*	*	**			*	*	*	7
11	Mussack et al. 2002	Cohort	*	*	*	**			*	*	*	7
12	Biberthaler et al. 2006	Cohort	*	*	*	**			*	*	*	7
13	David et al. 2017	Cohort	*	*	*	**			*	*	*	7
14	Mozaferi et al. 2019	Cross-sectional	*	*	*	**			**	*	*	9

*: meets the criteria

Seidenfaden et al., 2021 concluded that the diagnostic accuracy of GFAP cannot be validated because of the high cut-off value of the tests used.

Conclusion

Both S100B and GFAP is good indicator to predict the occurrence of the intracranial lesion in mTBI. S100B is more learned than GFAP and many of the studies suggest that S100B as a screening tool will reduce the cost of unnecessary CT scans. On other hand, GFAP is less studied than S100B but shows promising results in detecting intracranial lesions. More studies need to be done on both S100B and GFAP with more uniform methodologies to further validate the potential S100B and GFAP for detecting intracranial lesions in mTBI.

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