NEUROPHYSIOLOGY AND GENETICS OF BURNING MOUTH SYNDROME

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Conflict of interest

No conflicts of interest.

Significance

The results confirm earlier findings of neuropathic pain in BMS. The DRD2 957 C>T genotype influences perception and experience of clinical pain in BMS.

Abstract

Background and aims

Neuropathic mechanisms are involved in burning mouth syndrome (BMS), and variation of the dopamine D2 receptor (DRD2) gene contributes to experimental pain perception. We investigated whether neurophysiologic findings differ in

BMS patients compared to healthy controls, and whether 957C>T polymorphism of the DRD2 gene influences thermal sensitivity or pain experience in BMS.

Methods

Forty-five BMS patients (43 women), mean age 62.5 years and 32 healthy controls (30 women), mean age 64.8 years participated. Patients estimated pain intensity, interference, suffering and sleep with Numeric Rating Scale. Blink reflex tests of the supraorbital (SON), mental (MN) and lingual (LN) nerves, and thermal quantitative sensory testing were done. The results were analysed with ANOVA. DRD2 gene 957C>T polymorphism was determined in 31 patients and its effects on neurophysiologic and clinical variables were analysed.

Results

Cool (p=0.0090) and warm detection thresholds (p=0.0229) of the tongue were higher in BMS patients than controls. The stimulation threshold for SON BR was higher in patients than in controls (p = 0.0056). The latencies of R2 component were longer in BMS patients than in controls (p=0.0005) at the SON distribution. Habituation of SON BR did not differ between the groups. The heat pain thresholds were highest (p=0.0312) in homozygous patients with 957TT, who also reported most interference (p=0.0352) and greatest suffering (p=0.0341). Genotype 957CC associated with sleep disturbances (p=0.0254).

Conclusions

BMS patients showed thermal hypoesthesia within LN distribution compatible with small fibre neuropathy. The DRD2 957C>T genotype influences perception and experience of BMS pain.

Introduction

Primary burning mouth syndrome (BMS) is characterised by persisting burning pain of the oral mucosa, ranging from mild to intense (Grushka et al., 1987; Bergdahl and Bergdahl, 1999; Forssell et al., 2012) and impacting quality of life (Souza et al., 2011). The diagnosis is made by excluding other local and systemic factors that may cause secondary burning pain within the oral mucosa (Markman and Eliav, 2013; McMillan et al., 2016).

There is evidence for several neuropathic mechanisms associated with BMS. Studies using blink reflex (BR) and thermal quantitative sensory testing (QST) support neuropathic aetiology. Higher stimulation thresholds of the BR suggest dysfunction of the tactile sensory fibres at SON distribution, outside the intraoral pain sites (Jääskeläinen et al., 1997). Furthermore, BR abnormalities are found in 20% of patients, indicating subclinical brainstem pathology or peripheral trigeminal neuropathy of the lingual or mandibular nerves (Forssell et al., 2002). Thermal QST abnormalities, mostly hypoesthesia, are found in patients when results are compared with laboratory reference values (Forssell et al., 2002) or healthy controls (Ito et al 2002; Mo et al., 2015). These findings indicate either peripheral small fibre neuropathy or deafferentation of the central trigeminal thermal pathways. Further evidence for focal small fibre neuropathy in BMS comes from neuropathological studies showing decrease in epithelial nerve fibre density (ENFD) of the tongue mucosa (Yilmaz et al., 2007; ; Puhakka et al., 2016). However, as thermal QST and ENFD are age dependent (Kaplan et al., 2011, Holland et al. 1997), more rigorously controlled studies are warranted.

There is also evidence of central nervous system involvement in BMS. Habituation of the BR, which is under dopaminergic control (Basso et al., 1996), has been found to be deficient in 20% to 36% of patients (Jääskeläinen et al., 1997; Forssell et al., 2002), and PET studies have demonstrated low striatal dopamine levels in BMS (Jääskeläinen et al., 2001; Hagelberg et al., 2003). This finding may, in part, explain the perception of pain in BMS, as there are several lines of evidence that the dopaminergic system and striatal dopamine D2 receptors (DRD2) have an important role in central pain and its modulation (Hagelberg et al., 2003; Jääskeläinen et al., 2014; Martikainen et al., 2018).

DRD2 gene 957C<T polymorphism has been shown to influence both innocuous and noxious thermal detection thresholds in healthy subjects, being lowest in 957TT homozygotes (Jääskeläinen et al., 2014). Neuropathic pain patients with the homozygous 957TT genotype report more severe pain than patients with other genotypes (Jääskeläinen et al., 2014). Polymorphism altering catechol-O-methyltransferase (COMT val158met) has also been associated with TMD pain (Diachenko et al., 2006; Smith et al., 2011), but is not consistently associated with neuropathic pain (Huuhka et al., 2008).

The aim of this study was to confirm with rigorously controlled design our earlier findings in BMS by comparing the findings in BR and thermal QST studies to age- and sex-matched healthy controls. The second aim was to test whether DRD2 gene 957C>T or COMT val158met polymorphisms influence pain sensitivity or experience in BMS.

Methods

Subjects

The subjects of this prospective controlled study consisted of 45 BMS patients (mean age 63.8, range 45–82, 43 women) referred to the Department of Oral Diseases at Turku University Hospital who had not participated in any of our previous studies. Thirty-two age- and sex-matched healthy volunteers were used as controls (mean age 64.8, range 48–84, 30 women).

An experienced orofacial pain specialist examined the patients carefully and made the diagnosis according to valid criteria for BMS that are compatible with the current diagnostic criteria established by the International Headache Society (IHS 2018). Patients with mucosal lesions, candida infection or hyposalivation were excluded. None of the patients had abnormalities in the haematological screening (blood count, levels of fasting blood glucose, B12-vitamin, folate, antinuclear antibody values). Details about BMS pain, such as duration, pain location and possible laterality were registered and are shown in Table 1. Patients were asked to give an estimate regarding the mean highest and lowest pain intensities during the last 6 months using NRS from 0 to 10 (0=no pain, 10=worst possible pain). Interference, suffering and sleep disturbances caused by the pain were also inquired using NRS from 0 to 10 (0=not at all, 10=very much). The medications were registered.

The controls were mainly recruited from different activity groups for the elderly. They had no diagnosed neurological diseases or any serious mental problems or chronic pain conditions. Persons with facial pain, trauma or operations in the orofacial area were also excluded. All patients and control subjects underwent clinical neurophysiologic BR and psychophysical thermal QST examinations of the trigeminal nerve distributions. The participants gave their written consent. All patients were asked to give blood for genetic testing but only thirty-one were willing to do so .The studies were performed according to the Declaration of Helsinki. The ethical committee of Turku University Hospital approved the study protocol. All subjects provided written informed consent.

Neurophysiologic methods

Blink reflex (BR)

The BR responses were recorded bilaterally with surface electrodes on both orbicularis oculi muscles while the patients were sitting with their eyes open in a quiet room, using a small bipolar electrode for stimulation (13L35 Medtronic Functional Diagnostics A/S, Skovlunde, Denmark) and an eight-channel electromyography device (EMG) (Viking IV, Nicolet Biomedical Instruments, Madison, WI, USA) for recording and analysing the reflex responses. The supraorbital (SON), mental (MN) and lingual (LN) nerve distributions were stimulated. The stimulus intensity was gradually increased in 1 mA steps and adjusted to evoke both R1 and R2 responses at the SON distribution. About the same intensity was used on both sides. At each distribution, out of eight trials, the BR response with the shortest latency of the R2 components was used in the analyses. The latencies of the ipsilateral R1 and R2 components as well as stimulus intensities to evoke consistent responses were registered and compared with those of healthy controls.

The habituation of BR, i.e., the area decline of consecutive ipsilateral R2 (R2i) components compared to the first R2i component of the trial, was recorded with eight repeated stimuli given at 1 Hz intervals separately on both sides to the SON. The habituation index is the serial number of the trial first showing at least 50% decrement of the R2 area. These indices were registered and compared between the patient and the control subject groups. The recording of the BR has been reported in detail elsewhere (Jääskeläinen and Peltola, 1994; Kimura, 2001; Forsell et al., 2002; Jääskeläinen, 2004).

Thermal quantitative sensory testing (QST)

The thermal detection thresholds for cool, warm and heat pain were measured within the LN distribution of all patients and controls. The Termotest device (Somedic Sales AB, Hörby, Sweden) was equipped with a small, hand-held, rectangular probe (9x9mm^2) specially constructed for stimulating the facial area. The thermode consists of Peltier elements that either cool or warm up linearly depending on the direction of applied electric current. The maximum temperature range was set to 10–50 °C for cool detection threshold (CDT) and warm detection threshold (WDT), and to 10–55 °C for heat pain threshold (HPT) measurements, while the baseline temperature was 30 °C. The rate of linear temperature change was 1 °C/s. The subjects were instructed to press the switch button immediately when they perceived a change in temperature (cooling or warming), and when they felt the warm stimulus becoming painful. The detection thresholds were recorded as the change (in °C) from baseline temperature. The method is described in detail elsewhere (Forssell et al., 2002; Teerijoki-Oksa et al., 2003; Jääskeläinen et al., 2005).

The classical method of limits (Fruhstorfer et al., 1976) was applied. Five series of increasing intensities were given for each threshold measurement. After deleting the highest and lowest values, the mean of the remaining three values was calculated and used as the sensory detection threshold. The CDT was measured first, then WDT and finally HPT. The threshold values of the BMS patients were compared with those of the healthy subjects. The pre-pain range, i.e. the difference between HPT and WDT, was also calculated to assess possible warm allodynia.

All BR and QST studies were performed by experienced laboratory technicians familiar with these methods. All patients and control subjects co-operated well despite the advanced age of some subjects.

DNA analyses

Thirty-one of the BMS patients were genotyped to dopamine system-related genetic polymorphism for COMT Val158Met (GenBank NM_000754.3:c.472G>A, rs4680) and DRD2 gene 957C>T (GenBank NM_000795.3:c957C>T, rs6277) polymorphisms according to Jääskeläinen et al., 2014. Briefly, after DNA extraction from peripheral leucocytes, the polymorphisms were determined in separate PCR-RFLP runs, and the fragments were analysed with an agarose gel electrophoresis for genotyping. As a positive and negative control for PCR and restriction enzyme cut assessment, sequenced human standard DNA samples were used.

Statistical methods

Power estimation

In sample size calculation we used means and standard deviations of CDT, WDT and HPT in BMS patients and healthy controls (Mo et al., 2015). With 80% power with a two-tailed test at 5% level, twelve to twenty-seven participants would be required.

Blink reflex and thermal quantitative sensory testing were analysed using the general linear mixed model with repeated measures. Group or DRD2 957 C>T genotype was included in the model – when appropriate – as a between-subjects factor and side as a within-subjects factor. Both main and interaction effects were included in all models. The differences between DRD2 957 C>T genotypes were constructed by contrast. Differences are given as mean ± SE with 95% CIs. In all quantitative statistical analyses, the validity of the models was checked by residual

analyses. Associations of habituation of the blink reflex and other dichotomous variables between the groups were analysed by Chi-square or Fisher's exact test. All calculations were performed with SAS software (SAS Institute Inc., Cary, NC, USA).

The gender distribution of the present BMS patient material is skewed, in line with the previously reported female to male ratios in BMS (Jääskeläinen and Woda 2017). However, as there were less men than women in the patient group, the statistical analyses were performed for the whole group of patients and, additionally, after excluding the small subgroup of men. This did not affect any of the results, so we report here the results for the whole group of BMS patients. All results of the ANOVA analyses are given as the estimates of mean (EM) and its standard error (SE).

Results

Clinical findings

Demographic data and clinical characteristics of the BMS patients are presented in Table 1. Four (9%) of the 45 patients had pain also elsewhere in their body. Five (11%) patients had medicated hypothyreosis, with normal TSH levels. Thirty-four (76%) of the patients estimated sleep disturbances caused by pain to be less than five on the NRS scale, and only six (13%) suffered from more severe sleep disturbances. Patients reporting disturbed sleep also reported more suffering because of pain (P=0.0003).

In the control group, 22 subjects used no medications. Ten control subjects used blood pressure medication and six used cholesterol-lowering medication. Two control subjects used thyroxin and three used an antidepressant.

Neurophysiologic test results

Blink reflex

The stimulation threshold for BR at the SON distribution was higher in BMS patients (EM 12.7mA SE 0.5) than in control subjects (EM 10.6mA, SE 0.6; p=0.0056).

The latencies of the BR R2i component were also longer in BMS patients (EM 36.4 ms, SE 0.5) than in healthy subjects (EM 33.3 ms, SE 0.6; p=0.0005) at the SON distribution. For the MN, there were no statistically significant differences in the R2i latencies between BMS patients (EM 42.6 ms, SE 0.7) compared to the control group (EM 41.5 ms, SE 0.8; p=0.3076). The findings were similar concerning the LN distribution R2i latencies (EM 46.4ms, SE. 1.2 vs. EM 43.3 ms, SE. 1.2; p=0.0700).

The stimulation threshold of the SON for consistent BR responses was positively associated with the NRS score for minimum pain intensity (F=5.28, p=0.0272); patients with higher minimum pain levels needed higher stimulus intensities. Positively associated with minimum pain intensity were also the latencies of the SON BR (F=5.64, p=0.0227) and MN BR (F=8.66, p=0.0058). The longer the R2i component latency, the higher the baseline minimum pain intensity score.

The habituation of the blink reflex did not differ between the groups. The use of benzodiazepines or other drugs with central nervous system effects did not influence the stimulation thresholds or habituation of the SON BR, nor the latencies of the BR at any trigeminal distribution.

Thermal QST

CDT was elevated in BMS patients (EM 5.4 °C, SE. 0.5) compared to control subjects (EM 3.1 °C, SE 0.7; p=0.0090). WDT was also higher in BMS patients (EM 11.5 °C, SE 0.7) than in healthy subjects (EM 9.0 °C, SE 0.8; p=0.0229). Benzodiazepines had no effect on CDT (EM 3.3 °C, SE. 1,7; p=0.0663) or WDT (EM 2.1 °C, SE 1.9; p=0.2771).

There was no difference in HPT in the patients (EM 17.0 °C, SE. 0.5) compared to control subjects (EM 17.1 °C, SE. 0.6; p=0.9660). The pre-pain range was narrower in the BMS patients (EM 5.6 °C, SE. 0.6) than in controls (EM 8.3 °C, SE. 0.7; p=0.0024) because of higher WDT in BMS patients.

Genetic polymorphism

Nine of the BMS patients (29%) were 957TT homozygotes, 17 (55%) were 957CT heterozygotes and 5 (16%) were 957CC homozygotes. This frequency distribution does not differ from that of the general Finnish population (TT=31%, CT=48%, CC=21%) (Jääskeläinen et al., 2014). Pain intensity of less than five on the NRS was reported by 3 (16.7%) of TT, 11 (61.6%) of CT, and 4 (22.2%) of CC patients. Intensities of greater than five were reported by 3 (42.9%) of TT and 4 (57.1%) of CT. None of the CC patients reported pain greater than 5.

Table 2 shows the results of the ANOVA analyses concerning associations between the DRD2 gene 957C>T polymorphism and thermal QST findings, as well as subjective ratings of BMS pain. Patients with 957TT showed the highest HPT (p=0.0312) but there were no DRD2 genotype effects on CDT (p=0.5037) or WDT (p=0.3572) measures (Table 2). Patients with 957TT genotype reported the highest interference by pain in daily life (p=0.0352) and the most severe suffering (p=0.0341). On the other hand, patients with 957CC reported the most sleep disturbances (p=0.0254) (Table 2).

COMT Val158Met polymorphism had no influence on pain experience or other pain-related clinical variables in these BMS patients.

Discussion and conclusion

This study on primary BMS patients, meticulously diagnosed in line with the current criteria (IHS 2018) and using age- and sex-matched control subjects, revealed abnormalities both within the trigeminal large and small fibre systems as well as in the trigeminal brainstem complex. Negative neurophysiologic signs indicating decrease in function of the Aβ fibres extra-segmental to the intraoral pain site included increased stimulation thresholds and prolonged latencies of the R2 component of the supraorbital nerve blink reflex in BMS patients. Within the symptomatic intraoral area, thermal QST showed signs of focal loss of function in BMS patients. DRD2 gene 957C>T polymorphism seemed to influence thermal pain perception and experience of pain also in BMS patients. The heat pain detection thresholds were highest in patients with 957TT genotype, who also reported the most interference in daily life and suffering caused by BMS pain.

The results confirm most findings of our earlier studies, in which laboratory-specific reference values were used to determine the proportion of abnormal test findings in BMS patients. In line with our previous data (Jääskeläinen et al., 1997; Forssell et al., 2002), also the present results indicate neuropathic alterations at different levels of the nervous system in BMS. Higher stimulus intensities were needed to elicit the early R1 component of the blink reflex in BMS patients compared to healthy controls subjects, indicating somatosensory alterations within the extraoral trigeminal distributions in BMS. In line with this, the significantly longer latency of R2 at the SON distribution found here and in earlier BR studies (Jääskeläinen et al., 1997; Forssell et al., 2002) suggests more widespread trigeminal functional disturbance in BMS patients. This may be due to the fact that clinically similar primary BMS may be caused by peripheral trigeminal neuropathies extending outside the lingual nerve distribution as well as by trigeminal brainstem lesions (Forssell et al., 2002; Jääskeläinen, 2012; Jääskeläinen and Woda, 2017). Although some reports have claimed BMS is a pure, focal small fibre neuropathy (Lauria et al., 2005; Yilmaz et al., 2007), the present results indicate a change also in the non-nociceptive tactile sensory function, at least in some BMS patients, since both the R1 and R2 components of the BR are mediated via mechanoafferent Aβ-fibres. This extrasegmental disturbance may reflect a subclinical, more extensive trigeminal neuropathy in BMS, or even a widespread peripheral neuropathy that has also been suggested to be related to BMS (Lauritano et al., 1998; Puhakka et al., 2016). On the other hand, chronic pain condition such as BMS might cause an increase in the threshold and prolongation of the latencies of polysynaptic

brainstem reflex by means of increased tonic activity in the endogenous top-down inhibitory systems, similarly as distant pain acts in a conditioned pain modulation test (Yarnitsky et al. 2014; Nasri-Heir et al., 2018).

In contrast with some earlier observations, this first properly controlled neurophysiologic study on primary BMS found no significant difference in the habituation of the BR between the patients and a matched control group. It seems that although individual BMS patients may show abnormal habituation of the BR (Jääskeläinen et al., 1997; Forssell et al., 2002), deficient BR habituation occurs to same extent in healthy subjects of same age group. The habituation of the BR is under descending dopaminergic control (Basso et al. 1996), and as dopamine activity has been reported to decline with age (Kaasinen and Rinne, 2002), no significant between-group difference emerged in the present study using a proper age-matched control group with higher mean age compared to that of the normal reference population used in our previous studies (Forssell 2002; Jääskeläinen 1997). A decreased inhibitory tone exerted by endogenous dopamine-opioid system may be involved in the pathogenesis of BMS (Jääskeläinen et al., 1997; 2001; 2014; Jääskeläinen 2012; Jääskeläinen and Woda 2017).

The striatal dopamine system has been suggested to be involved in the modulation of pain (Jääskeläinen et al., 2014; Martikainen et al., 2018), possibly via triggering the endogenous opioid system (Jääskeläinen et al., 2014; Lamusuo et al., 2017). Furthermore, repetitive transcranial magnetic stimulation (rTMS) potentiates habituation of the BR reflex in healthy subjects (Lamusuo et al., 2017), by releasing dopamine and opioids (Strafella et al., 2001; 2004; Lamusuo et al., 2017) and simultaneously increasing pain detection thresholds (Valmunen et al., 2009; Jääskeläinen et al., 2014). At menopause there is a decline in gonadal steroids, e.g. estradiol and progesterone. Reduction of sex hormones disturbs synthesis of neuroprotective neurosteroids that have an important role in recovery after neuronal damage. This may affect the function of small fiber neurons and striatal dopaminergic neurons that are especially vulnerable to toxic agents (for a more detailed discussion, c.f. Jääskeläinen and Woda 2017, Savica et al. 2016). Resulting dopamine deficiency could act as a trigger in the development of BMS because of failing endogenous inhibitory control (Jääskeläinen and Woda 2017).

In agreement with the present findings, thermal hypoesthesia at the tongue mucosa has been reported in most previous studies using appropriately sized small thermodes and age-matched controls. Both CDTs and WDTs have rather consistently been found to be higher in BMS patients compared to control subjects (Forssell et al., 2002; Mo et al., 2015; Puhakka et al., 2016). These thermal QST findings of loss of function are compatible with the concept of BMS as a neuropathic pain condition due to focal small fibre neuropathy (Lauria et al., 2005; Yilmaz et al., 2007; Puhakka et al., 2016). Only one study, using controls ten years younger than patients, has reported lower CDT and WDT in BMS patients than in controls, suggesting thermal hyperesthesia (Yilmaz et al., 2016). Despite rather consistent reports on hypoesthesia to innocuous thermal stimuli, subgroups of BMS patients have shown both hyperalgesia and hypoalgesia in heat pain testing (Forssell et al., 2002; Ito et al., 2002; Gremeau-Richard et al., 2010; Yilmaz et al., 2016; Mo et al., 2015). In the present study, no significant differences in HPT between BMS patients and control subjects were found in the group-level comparisons. However, the pre-pain range was significantly narrower in BMS patients, because of the thermal hypoesthesia reflected in high WDT. The fact that primary BMS patients may show opposite types of thermal pain detection abnormalities, either gain or loss of function, render group-level comparisons of these QST findings susceptible to random effects that may explain some of the controversies between earlier reports (for reviews, c.f. Jääskeläinen, 2012; Jääskeläinen and Woda, 2017).

The present discovery of more pronounced affective dimensions of pain experience in 957TT homozygote subjects is in line with the previous observation that neuropathic orofacial pain patients with the 957TT genotype report the most severe pain in the NRS scale (Jääskeläinen et al., 2014). However, in healthy subjects, the 957TT genotype correlates with the lowest thermal detection thresholds (both innocuous and noxious; Jääskeläinen et al., 2014), whereas here, the BMS patients with the DRD2 957TT showed the highest pain detection thresholds, i.e., the most pronounced heat and cold pain hypoalgesia, most often in the form of analgesia. This may be explained in the light of our observation in healthy subjects: individuals with the 957TT genotype show a significant increase in HPT after analgesic rTMS, which does not occur in the other two genotypes (Jääskeläinen et al., 2014). Thus, the 957TT

genotype seems to correlate with a more prominent or efficient neuroplastic cortical response, probably including quick cortical reorganization (Flor et al., 1995; Maihofner et al., 2004) following therapeutic neuromodulation. Accordingly, higher tendency to neuroplasticity in BMS patients with DRD2 genotype 957TT, also maladaptive, might lead to more severe thermal hypoesthesia/anesthesia via more prominent cortical reorganization in relation to intensity of BMS pain. Increased central neuroplasticity has been implicated as playing an important role in chronic neuropathic pain associated with CRPS (complex regional pain syndrome) and post-amputation pain (Flor et al., 1995; Maihofner et al., 2004; Juottonen et al., 2002), as well as in extra-segmental spread of thermal hypoesthesia in chronic orofacial pain (Jääskeläinen et al., 2005). In line with scarce earlier data (Huuhka et al., 2008; Jääskeläinen et al., 2014; Lindholm et al., 2015) COMT Val158Met polymorphism did not correlate with chronic orofacial pain.

The patients were diagnosed according to valid criteria for BMS compatible with the current diagnostic criteria established by the International Headache Society (IHS 2018). In this study we confirmed earlier findings indicative of focal small fiber neuropathy within a new group of BMS patients compared to a strictly matched control group.

One disadvantage of this study is its small sample size in considering the genetic analyses. Nevertheless, DRD2-related 957C>T polymorphism seems to influence pain sensitivity or experience in BMS, while COMT Val158et polymorphism did not shows such associations. This is in line with our previous findings in another group of neuropathic orofacial pain patients (Jääskeläinen et al., 2014). Further research is needed to confirm these findings.

Conclusions

BMS is still a challenging disorder since its aetiology is diverse. In this study we confirmed earlier findings of focal small fibre neuropathy. The DRD2 gene-related polymorphism 957C>T seems to influence sleep, pain sensitivity and the experience of pain in BMS patients.

Author contributions

Heli Forssell, Satu Jääskeläinen and Ullamari Pesonen conceived and planned the experiments. Antti Puhakka gathered the subjects. Ullamari Pesonen carried out the gene tests, and Arja Virtanen performed the statistical analyses. Marina Kolkka participated in the analysis of the results and wrote the manuscript with support from Heli Forssell and Satu Jääskeläinen, who also supervised the project. All authors contributed to the final version of the manuscript.

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