Painful Traumatic Trigeminal Neuropathy: An Open Study on the Pharmacotherapeutic Response to Stepped Treatment

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Aims: To evaluate pharmacotherapeutic success in patients with painful traumatic trigeminal neuropathy (PTTN) and to identify patient or pain characteristics that may predict treatment outcome. Methods: Pharmacotherapy was instituted for PTTN patients and was based on widely accepted protocols for neuropathic pain and conducted in an open fashion. Outcome was assessed by employing prospective diaries recording pain intensity measured with an 11-point (0 to 10) verbal pain score (VPS). Individual characteristics in the patients and their influence on outcome were analyzed. Treatment results in the PTTN patients were compared with those in classical trigeminal neuralgia (CTN) patients, who were used as a comparative cohort. Data were analyzed with a Pearson chi-square test for nominal variables and with an independent samples t test or analysis of variance for continuous variables. Results: A total of 145 patients were included: 91 with PTTN and 54 with CTN. In PTTN patients, 11% had a ≥ 50% reduction in pain intensity. Higher VPS scores in the PTTN patients were associated with a significantly reduced response to therapy ($P = .03$). No other pain-related or demographic parameters were associated with treatment outcome in the PTTN patients. Also the response rate of PTTN patients was significantly inferior to that of CTN patients, 74.1% of whom attained a significant reduction in pain intensity ($P < .001$). Conclusion: This study underpins the poor pharmacotherapeutic prognosis of PTTN. The results support findings on neuropathic pain in other sites and point to the need for further research and reexamination of current PTTN treatment protocols.

Key words: antidepressants, antiepileptic drugs, orofacial pain, trigeminal neuralgia

Chronic neuropathic pain can result from disease or lesions affecting the function of the peripheral and/or central sensory nervous system. Thus, injury to the trigeminal somatosensory system at any level, ie, peripheral nerve, ganglion, or sensory (dorsal) root or central structures can induce chronic neuropathic pain. Facial pain following injury to the trigeminal nerve is poorly defined and has several names and definitions. Deafferentation pain, phantom tooth pain, atypical odontalgia, atypical facial pain, anesthesia dolorosa, posttraumatic neuralgia, and persistent idiopathic facial pain have all been used to describe facial pain following various degrees of regional trauma. Painful traumatic trigeminal neuropathy (PTTN) is a new definition and is employed in the present article.

Classical trigeminal neuralgia (CTN), or tic douloureux, has been extensively studied and was used in this study as a comparison to PTTN. Much of the available CTN data suggests that the dorsal root entry zone (DREZ) may be damaged by its prolonged contact with a blood vessel. The DREZ is the central extension of the primary afferent, and therefore DREZ lesions are considered peripheral. In this respect, CTN and PTTN share some pathophysiologic features. CTN is extremely severe and is characterized by short-lasting attacks with typical triggering mechanisms and a refractory period. Clinically, PTTN
and CTN are different neuropathic pains. However, since they share some pathophysiologic similarities (both follow injury to the trigeminal nerve), they make suitable comparators.

Due to the paucity of data on PTTN’s pharmacotherapeutic response, the aim of this study was to evaluate pharmacotherapeutic success in patients with PTTN and to identify patient or pain characteristics that may predict treatment outcome.

**Materials and Methods**

This project was designed as a prospective cohort study in which the treatment results of the subjects of interest (PTTN) would be compared to those of patients suffering from CTN. The clinical phenotype of PTTN patients has been recently described.14

**Recruitment: Inclusion/Exclusion Criteria**

Patients were collected from the Orofacial Pain Clinic at the Faculty of Dentistry, Hebrew University–Hadassah in Jerusalem. The service acts as a tertiary referral center and serves all of Israel. Most patients were referred by a general practitioner or medical/dental specialist, with a few being self-referrals.

Inclusion criteria included a complaint of persistent facial pain, diagnosed as either CTN, based on the definition of the International Headache Society (IHS),11 or PTTN, as recently defined.14 “Persistent” refers to pain that is present for a minimum period of 3 months.

For the current study, the diagnosis of PTTN included the presence of pain that was clearly associated with a traumatic event (historically or otherwise demonstrable) and located in the vicinity of the initiating injury or its distal dermatome. Positive and/or negative neurologic manifestations should be verifiable by gross and/or advanced techniques, such as neurophysiological or quantitative sensory testing.14

No patients included were on active therapy at the initial intake. Nonpainful neuropathies (ie, sensory deficits with no pain) were excluded. All other patients attending the pain clinic who had temporomandibular disorders or other orofacial pains were also excluded.

In this manner a total of 145 patients were included: 91 with PTTN and 54 with CTN.

**Clinical Assessment at Pretreatment Visit**

The intake form employed in the Orofacial Pain Clinic includes a pain history that records pain location, quality, severity (on an 11-point verbal pain scale [0 to 10 verbal pain score or VPS]),14,18 frequency, and attack duration, as well as age of onset, associated features, analgesic drug use, and aggravating or alleviating factors. Pain quality was established by asking the patients to choose one or more of the following descriptive terms: electrical, stabbing, throb-bing, pressure, burning, or any combination of the five terms. These five arbitrary terms are in routine use in the clinic to provide rapid assessment of pain quality.14,18,19 Additionally, these were individually coded so that specific combinations of qualitative descriptors could also be analyzed.

To assess the temporal patterns, patients were allocated to one of three groups based on attack frequency and duration: “daily” for patients with short and daily attacks of pain (> 15 days a month) lasting less than 4 hours, “episodic” for patients with attacks of pain lasting less than 4 hours that occurred on <= 15 days monthly, and “continuous” for patients with daily constant pain (attacks > 4 hours or continuous). This was based on the authors’ previously published methodology.20 Patients with primarily paroxysmal daily pain who also reported a constant background pain were coded as having concomitant “background pain.” Patients were asked to report pain duration representing that of a typical attack. The presence of autonomic signs (tearing, redness, rhinorrhea, and swelling) was noted.

Patients were also asked whether the pain specifically waked them from sleep; a standardized question was used: “Does your pain wake you from sleep?” Answers were carefully interpreted so as to ensure that the patient was reporting awakening specifically related to pain.21 Additionally, demographic data (sex, ethnicity), health status, and medication or history of other therapeutic intervention were recorded. The intake was applied for a period of 3 years to all patients attending the clinic. The institutional review board approved the analysis and use of collected data and patients consented to the use of their data.

The clinical assessment included a routine physical examination of the head and neck and the dental and periodontal tissues, as well as a gross examination of the cranial nerves. An attempt was made to identify trigger points/areas (which when pressed, caused onset of severe pain that spread beyond the area of stimulation).

The masticatory apparatus (temporomandibular joints and masticatory muscles) and neck muscles were examined for sensitivity to palpation as previously described.14 For muscle tenderness, a total tenderness score was calculated.21,22 The muscle tenderness score, also known as the total tenderness score in the literature, is commonly used in headache practice for the assessment of pericranial muscle tenderness and adds valuable information.22

Diagnostic imaging was requested for CTN cases (brain and brainstem computerized tomography [CT] or magnetic resonance imaging/angiography) and for other diagnoses as needed. Additionally, areas
adjacent to the nerve injury were imaged (plain radiography, CT).

**Treatment Protocol**

The protocol employed for PTTN (Fig 1) was based on accepted protocols published in the literature.\(^{23-27}\) Initial therapy is with amitriptyline (or nortriptyline), and it was instituted in this study with the dose titrated to clinical response unless there were medical contraindications or there was no response in 6 to 8 weeks of therapy. In these cases gabapentin (or pregabalin) was employed. Lack of response was an indication for combined therapy (if the medical history allowed this). In combined therapy, duloxetine is often used instead of amitriptyline due to its better safety profile. Failure of the drug combinations is an indication for opioid therapy. Patients with PPTN were not referred for cognitive behavioral therapy (CBT) so the isolated effects of pharmacotherapy could be assessed.

CTN cases are routinely initially prescribed carbamazepine, which was instituted in this study with the dose titrated to clinical response. Severe side effects at therapeutic doses were an indication to introduce oxcarbazepine instead, or reduce the carbamazepine dose and add baclofen. Switching to gabapentin (or pregabalin) is the next step in therapy (see Fig 1).

**Treatment Outcome**

Patients received a 28-day diary to record pain frequency, duration, and severity twice daily by employing a VPS of 0 (no pain) to 10 (maximal pain imaginable). These diaries were used as part of the diagnostic process, follow-up, and treatment outcome assessment.

A minimum of 3 months of active treatment was required for assessment. Assessment of treatment results was based on the reduction of pain severity (as a percentage) at the 3-month recall, relative to the baseline reported values. Too many patients had continuous pain to allow the use of pain frequency as a reliable tool. Two outcome groups were defined. The no-response group (pain was not improved or improved by less than 50%) included all patients lost to follow-up who were considered treatment failures. The VPS value was the last recorded in their files. The second group included those whose pain was significantly reduced (significant response), defined as a reduction of 50% or more in their VPS.

**Statistical Analyses**

Data were tabulated and analyzed with SPSS (IBM-SPSS, version 19 for Macintosh) with significance (alpha) set at .05 (two-tailed). Interactions between nominal variables were analyzed with a Pearson chi-square
$$\chi^2$$ test. Differences between means in continuous variables underwent an independent samples t test. In selected situations, analyses of more than two independent variables were included, for which an analysis of variance (ANOVA) was used followed by pairwise comparisons with a Games Howell (GH) test.

**Results**

The average follow-up in patients who returned for treatment was 9 months (range 6 to 24 months). In the PTTN group, 31 of the 91 patients (34.1%) were lost to follow-up, 35 did not respond to therapy (38.5%), and 15 (16.4%) refused therapy. Only 10 (11%) of the PTTN patients obtained significant pain relief. Based on an "intent to treat" principle, the patients lost to follow-up were regarded as treatment failures. For statistical analyses, this resulted in 66 patients with "no response" and 10 patients with a "significant response."

In comparison, none of the 54 CTN patients was lost to follow-up and only 14 did not respond to therapy (25.9%). Significant pain relief (≥ 50%) was obtained in 40 (74.1%) of the CTN patients (Fig 2).

**Pain Characteristics in Relation to Treatment Success**

Basic demographic data for the PTTN patients, including sex, age of onset, duration of pain in months, and clinical data on temporal pattern, awakening due to pain, frequency and duration of pain attacks, unilateral versus bilateral location, background pain, presence of trigger points, autonomic or systemic signs, and the muscle tenderness score, are presented in Table 1. Other than for baseline VPS, no statistically significant differences in the above parameters were observed within the PTTN group when patients with no response were compared to patients with a significant response. Individual pain quality descriptors or specific combinations of these were not significantly related to outcome.

**VPS**

The statistically significant difference found in baseline VPS between the no-response group (8.0 ± 1.5) and the significant-response group (6.9 ± 1.6) ($t = 2.2, df = 74, P = .03$) raised an interesting question as to whether patients who have refused treatment reported a significantly different baseline VPS. Indeed, analysis revealed overall significant differences between VPS values in the patients who refused treatment (6.5 ± 2.2) and the no-response and significant-response patients (ANOVA; $F = 4.4, df = 2, P = .02$). Pairwise comparisons showed that only the refused-treatment group’s VPS was significantly lower than that of the no-response group’s VPS (GH; $P = .04$).

When PTTN patients were grouped into those treated with any antiepileptic drug (VPS 7.9 ± 1.5), any antidepressant (VPS 7.5 ± 1.8), and any combination of the two (VPS 8.2 ± 1.5), the VPS values between them were significantly different (ANOVA $df = 3, F = 3.5, P = .018$, GH all pairs $P > .05$). For this latter test, the single case treated with opioids was excluded.
Pharmacotherapeutic Protocol
First-line drugs employed in the treatment of PTTN were largely amitriptyline (n = 74, 81.3%) or gabapentin (n = 2, 2.2%). Amitriptyline alone was employed in 73 PTTN patients at a mean dose of 21 ± 9.7 mg (range 10 to 50 mg daily [d]) (Fig 3).

Table 1 Demographic Data and Pain Characteristics of Patients with Painful Traumatic Trigeminal Neuropathy (PTTN) According to Therapeutic Outcome

<table>
<thead>
<tr>
<th></th>
<th>No response (n = 66)</th>
<th>Significant response (n = 10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>42 (63.6%)</td>
<td>6 (60%)</td>
<td>.82</td>
</tr>
<tr>
<td>Age at onset (y)</td>
<td>45.6 ± 16.7</td>
<td>46.7 ± 13.0</td>
<td>.84</td>
</tr>
<tr>
<td>Disease onset (mo)</td>
<td>36.2 ± 60.5</td>
<td>29.2 ± 42.6</td>
<td>.73</td>
</tr>
<tr>
<td>Frequency (mo)</td>
<td>24.5 ± 7.5</td>
<td>23.4 ± 9.6</td>
<td>.68</td>
</tr>
<tr>
<td>Duration (min)</td>
<td>646.0 ± 713</td>
<td>1018.9 ± 959.4</td>
<td>.15</td>
</tr>
<tr>
<td>MTS</td>
<td>3.8 ± 5.7</td>
<td>4.3 ± 10.6</td>
<td>.81</td>
</tr>
<tr>
<td>VPS</td>
<td>8.0 ± 1.5</td>
<td>6.9 ± 1.6</td>
<td>.03</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>31 (47%)</td>
<td>3 (30%)</td>
<td></td>
</tr>
<tr>
<td>Episodic</td>
<td>2 (3%)</td>
<td>1 (10%)</td>
<td>.41</td>
</tr>
<tr>
<td>Continuous</td>
<td>33 (50%)</td>
<td>6 (60%)</td>
<td></td>
</tr>
<tr>
<td>Waken</td>
<td>25 (37.9%)</td>
<td>3 (30%)</td>
<td>.63</td>
</tr>
<tr>
<td>Unilateral</td>
<td>61 (92.4%)</td>
<td>10 (100%)</td>
<td>.37</td>
</tr>
<tr>
<td>Background pain</td>
<td>13 (19.7%)</td>
<td>2 (20%)</td>
<td>.98</td>
</tr>
<tr>
<td>Trigger points</td>
<td>5 (7.6%)</td>
<td>0 (0%)</td>
<td>.37</td>
</tr>
<tr>
<td>Autonomic signs</td>
<td>7 (10.6%)</td>
<td>0 (0%)</td>
<td>.28</td>
</tr>
<tr>
<td>Systemic signs</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
<td>.58</td>
</tr>
</tbody>
</table>

All percentages represent the proportion within the treatment response group. No statistically significant differences were observed between the two groups other than in the verbal pain score (VPS). MTS = muscle tenderness score.

Fig 3 Flow chart demonstrating therapeutic course of patients with painful traumatic trigeminal neuropathy (PTTN). Ami = amitriptyline, GBP = gabapentin, DUL = duloxetine, CBZ = carbamazepine, BCF = baclofen, PGB = pregabalin, SE = transferred due to side effects, NE = transferred due to no effect on pain. Double-headed arrows indicate fusion of two pathways.
Following therapeutic failure with amitriptyline, the antiepileptic drug used was gabapentin (n = 19) or pregabalin (n = 1). One patient received carbamazepine and baclofen. The mean gabapentin dose employed was 1,300 ± 380 mg/d (range 900 to 2,000 mg/d), while pregabalin was used at a mean daily dose of 225 ± 100 mg/d (range 150 to 300 mg/d).

A combination of amitriptyline and gabapentin was used in 11 patients; 6 after a trial with amitriptyline and 5 after a trial with gabapentin.

Duloxetine (dose 60 mg/d) was employed in two patients and nortriptyline (25 mg/d) in one patient who had side effects to amitriptyline; in one of these cases, opioid therapy was prescribed due to an insufficient therapeutic response.

CTN cases were all treated with an antiepileptic drug, 32 (59.3%) with carbamazepine (mean dose 530 ± 200 mg, range 200 to 800 mg/d). Carbamazepine was combined with baclofen in 3 (5.6%) cases. Oxcarbazepine was used in 4 cases at a mean dose of 900 ± 800 mg, (range 200 to 1,800 mg/d). Gabapentin (mean dose 1,680 ± 330 mg) or pregabalin (150 mg/d) was used in 12 cases (22.2%), and baclofen alone was used in 3 cases (5.7%, mean dose 35 ± 18 mg, range 15 to 50 mg/d) due to allergy to antiepileptic drugs.

With accepted standard of care protocols, the outcome of therapy was significantly better in the CTN patients than in the PTTN patients ($\chi^2 = 49.5, df = 1, P < .001$; Fig 2).

Discussion

The most prominent finding of this study was the recalcitrant nature of PTTN to standard pharmacotherapy. Only 10 patients (11%) had significant pain reduction. Even adopting a ≥ 30% improvement level as clinically significant,28,29 only about 25% of the patients would be included. This is in line with, but inferior to, results in studies of other neuropathic pains, such as postherpetic neuralgia, painful diabetic neuropathy, and painful spinal traumatic neuropathies, where a 20% to 40% response rate has been reported.30 The results for PTTN are in stark contrast to the initial response observed for CTN; 74% of CTN patients obtained significant pain reduction and only 26% reported no significant improvement. This is in agreement with data in the literature.31,32 The reasons for this marked difference are unclear.

Clinical Entities

PTTN has been increasingly observed in the authors’ clinic, possibly due to the multiplicity of surgical procedures, in particular placement of dental implants. Considering the extraordinary number of invasive dental procedures causing nerve injury, it is fortunate that most patients do not develop chronic neuropathic pain. Following injury to trigeminal nerve branches, chronic pain develops in about 3% to 5% of patients.33,34 This includes major injury such as zygomatic fractures and other head trauma,35 but also minor interventions such as endodontic therapy and the insertion of dental implants. The occurrence of peripheral neural damage may lead to persistent pain that is often disproportionate to the initiating trauma.

As recently described, PTTN is predominantly unilateral and limited to the involved dermatome. It is usually of burning, electrical, or stabbing quality and accompanied by positive or negative sensory signs.14,23 The term PTTN is new and has not been universally accepted. As described above, the same entity of neuropathic pain occurring after nerve injury has been described using a number of different terms.

The comparative group is CTN, a well-documented neuralgia whose pathophysiology mainly seems to involve damage to the DREZ.36 The histopathology of DREZ biopsies from CTN patients37 is similar to that seen in certain traumatic neuropathies,38 although the latter are certainly more varied and dependent on the degree of damage.

Treatment Outcomes and Predictors of Success

In pain management, a reduction of 50% or more in pain intensity and/or frequency is considered therapeutic success.28,29 In some neuropathic pain cases, 30% reflects meaningful pain relief.28 Standard pharmacotherapy is largely managed based on published protocols.26,39 To a large extent, these protocols depend on the antiepileptic drugs and the tricyclic antidepressants. CTN responds to antiepileptic drugs, particularly carbamazepine, which is still considered the drug of choice.32 Very few studies have dealt with the therapeutic response of traumatic neuropathies in general and trigeminal neuropathies in particular. For painful neuropathies, pharmacotherapeutic response rates of 20% to 40% have been reported, which is remarkably low.40,41

CTN is characterized by an initially good response to pharmacotherapy (70% of patients) but a predictable and progressive reduction in response: by 5 to 16 years, the response rate is around 20%, with 44% of patients requiring drug combinations or alternative medication.42,43

Examining various demographic characteristics of PTTN patients in the present study did not reveal a predictor of treatment success. However, higher VPS values were associated with a significantly reduced response to therapy, and patients who had refused treatment had the lowest VPS values.
Standard pharmacotherapy of neuropathic pain leads to improved quality of life, better sleep quality, and improved mood. However, pain intensity is reduced by only 20% to 40% and is usually accompanied by significant side effects, particularly at the higher doses often required in neuropathic pain. Based on current knowledge, neuropathic pain involves multiple and complex molecular mechanisms. Thus, the use of drugs with different modes and sites of action may theoretically lead to improved efficacy with reduced side effects. Indeed, the combination of gabapentin and morphine produced significant analgesia in patients with neuropathic pain (postherpetic neuralgia and diabetic neuropathy) at a lower dose than each drug separately. In patients with painful diabetic neuropathy who did not respond to gabapentin monotherapy, the addition of venlafaxine in a double-blind fashion resulted in significant pain improvement. Good-quality studies demonstrate superior efficacy of two-drug combinations. However, due to limited studies for any one specific combination, as well as other study factors (eg, limited trial size and duration), it is difficult to recommend any one specific drug combination for neuropathic pain.

The present study’s finding of an inverse correlation between baseline VPS values and treatment outcome suggests that an alternative treatment strategy could be designed for individual patients. Thus, in patients with a high baseline VPS (eg, > 8), combined therapy may be a better initial choice. This is based on the premise that combination therapies are more efficacious than monotherapy. In some ways this approach is similar to the stratified approach used to treat migraine and may offer advantages over the current “stepped” approach. However, this hypothesis needs to be tested in controlled trials.

Treatment Protocol

Standard pharmacotherapy is largely based on published protocols. To a great extent these protocols depend on the antiepileptic drugs and the tricyclic antidepressants. CTN responds to antiepileptic drugs, particularly carbamazepine, which is still considered the drug of choice. Tricyclic antidepressants (especially amitriptyline) have been extensively tested in neuropathic pains such as painful spinal traumatic neuropathies, painful diabetic neuropathies, and painful polyneuropathies. For these reasons, tricyclic antidepressants remain the first drug employed in the authors’ clinic for PTTN cases.

However, the tricyclic antidepressants have a number of bothersome side effects, including tiredness, weight gain, and mouth dryness. At doses of over 50 mg, cardiovascular problems may be particularly prominent. For these reasons, many patients refuse treatment following even one or two doses of a tricyclic antidepressant or do not return for follow-up. The newer antiepileptic drugs, such as gabapentin or pregabalin, have a lower side-effect profile, thus increasing their chances for success.

The lack of efficacy or side effects of tricyclic antidepressants was an indication in the present study to try gabapentin or pregabalin. Next, combinations of antiepileptic drug and tricyclic antidepressant families were used. The third line of therapy was opioids, which were used only once. The progression through the treatment protocol, or stepped approach, is the current recommendation.

Treatment of CTN relies upon the antiepileptic drug family, especially carbamazepine or oxcarbazepine. Rarely, other antiepileptic drugs, such as gabapentin or pregabalin, were used. Baclofen is an accepted second-line therapy for CTN, usually combined with carbamazepine but also used as monotherapy.

It is clear that current drug strategies are not inducing a high enough response rate for the treatment of PTTN. Additional therapies such as psychologic interventions were not tested in the present study but are likely to improve the prognosis. A possible criticism of the present study’s therapeutic approach is that, in some resistant cases, it did not more rapidly proceed to opioids. This is related to significant resistance on the part of the patients to receive opioids. Additionally, it is possible that under the present circumstances, the therapists involved may have been wary of prescribing opioids.

Study Limitations

The question arises as to whether the findings of this study are limited to the trigeminal region. The trigeminal nerve shows distinctive features in response to pain, both clinically and at the level of neuronal changes. This would suggest that therapy may also be different, although the therapeutic response of traumatically induced spinal neuropathic pain is similarly poor.

The current study was not blinded, theoretically allowing for clinician bias. Additionally, it was neither placebo-controlled nor a “head to head” comparative study. The lack of a placebo control does not allow an assessment of how much of the therapeutic effect was placebo and how much “true” drug effect. Placebo effects can often be quite large.

Finally, there was no psychosocial assessment performed. Although this was intentional to isolate the drug effects, in retrospect a baseline assessment may have revealed significant effects on outcome.
Conclusions

This study is one of the first to deal with the pharmacotherapeutic response of painful trigeminal traumatic neuropathies. The results arising from this study should lead to further research and reexamination of current PTTN treatment protocols. The poor outcome is a reflection of the limited number of drugs available, their limited efficacy for neuropathic pain, and their side-effect profile. There is a need for more efficacious and safer drugs for the treatment of neuropathic pain.

The results of this study emphasize that patients with high VPS values are less likely to improve significantly. As discussed, this may be an indication to change the philosophy from a stepped to a stratified care approach. However, this needs to be proven in a comparative study using the two different approaches.

Undoubtedly there is a need for an integrated therapeutic approach in PTTN. Pharmacotherapy on its own is clearly unsuitable, and future research should test the combined results of drugs with biopsychosocial and complementary approaches. Psychosocial assessment should form part of the baseline and follow-up assessment of chronic pain patients. In turn, supportive therapy may be of added value in affected patients undergoing prolonged therapeutic trials of various drugs.

Acknowledgments

The authors report no conflicts of interest related to this study.

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