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Original Article

Exploring the time course of painful post-traumatic trigeminal neuropathy: a pilot study

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Abstract – Patients suffering from painful post-traumatic trigeminal neuropathy (PTTN) often report circadian variations in pain. This pilot study aimed to assess the daily evolution of pain in patients fulfilling the following criteria: PTTN diagnosed based on ICHD-3 criteria; >18 years of age; no impairment in communication and signed informed consent. Primary study outcome was a self-declared quantitative assessment of pain intensity using an 11-point numerical scale (0–10) for 8 consecutive days. Impact on oral function and quality of life was also assessed, using psychometric questionnaires GOHAI and HADS. Eleven patients with PTTN were recruited (mean age: 66.1 ± 6.8 years old). Mean pain intensity was 3.6 ± 0.99. Mean pain intensity increased progressively and significantly during the day, from 1.8 ± 1.3 to 4.6 ± 2.3 ($p < 0.0001$). Mean HADS score was 7.8 ± 2.7. Mean GOHAI score was weak (35/60). In conclusion, PTTN seems to follow a circadian rhythm.

Introduction

Painful post-traumatic trigeminal neuropathy (PTTN) defines uni- or bilateral oral and/or facial pain, secondary to peripheral injury of the trigeminal nerve [1], following orthognathic surgery, facial trauma, tooth avulsions or endodontic treatments for instance. Pain is classically continuous, of variable -sometimes fluctuating- intensity, presenting as burning, pricking, crushing or electric-shock-like pain, often associated with positive (mechanical allodynia) or negative (hypoesthesia…) neurological signs [2]. Prevalence of PTTN varies between 0.5 and 12% of the general population [2–4]. In the absence of formalized guidelines, treatment of such neuropathic pain is similar to other spinal neuropathies, *i.e.* via the use of anticonvulsant and/or antidepressant drugs [5,6]. Unfortunately, such treatments are globally of limited efficacy and not without significant adverse effects [7]. Moreover, such drugs appear less effective in the treatment of trigeminal neuropathic pain as compared to their spinal counterpart [8].

Despite the important prevalence and suboptimal management of neuropathic pain, the means allocated to relevant pathophysiological research are clearly insufficient [9,10]. Nevertheless, understanding such underlying pathophysiology is of paramount importance to enable the development of new treatment options. Recent research aimed at defining the painful phenotype have led to the identification of specific clinical subgroups [11,12], and the proposal of new diagnostic categories. For instance, the pain profile of such patients, using quantitative approaches such as Quantitative Sensory Testing (QST) has been evaluated in numerous studies [13]. Conversely, the temporal phenotype has received little attention so far. However, there is evidence that periodic biological rhythms could be implicated in the development of pain [14,15], suggesting that studying the time course of pain could provide insight on underlying pathophysiological mechanisms. Mammals are indeed subject to circadian rhythms, under the control of two main systems: (1) a master clock located with the suprachiasmatic nucleus of the hypothalamus (SCN) and under the influence of retinal luminous information and (2) other circadian oscillators (peripheral clocks) located in almost every cell of the organism, but synchronized by the SCN [16]. The central circadian clock is comprised of several

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Table I. Patient selection criteria. ICHD-3 = International Classification of Headache Disorders 3rd edition (IHS 2018).

Inclusion criteria	Non-inclusion criteria
– Age >18 – Signed informed consent – Patient with health insurance – Patient with untreated orofacial pain or not relieved by over 3 months treatment – Patient fulfilling the criteria of painful post-traumatic trigeminal neuropathy (ICHD-3): – A. Facial and/or oral pain in the distribution(s) of one or both trigeminal nerve(s) and fulfilling criterion C – B. History of an identifiable traumatic event to the trigeminal nerve(s), with clinically evident positive (hyperalgesia, allodynia) and/or negative (hypaesthesia, hypalgesia) signs of trigeminal nerve dysfunction. The traumatic event may be mechanical, chemical, thermal or caused by radiation. – C. Evidence of causation demonstrated by both of the following: 1. pain is localized to the distribution(s) of the trigeminal nerve(s) affected by the traumatic event 2. pain has developed <6 months after the traumatic event – D. Not better accounted for by another ICHD-3 diagnosis	– Patient with orofacial pain efficiently treated with drugs – Patient refusing to participate in the investigation – Non adult patient – Patient with communication impairment – Patient participating in another investigation – Patient with no health insurance – Patient using a drug that might cause chronic orofacial pain (such as neuroleptics or conversion enzyme inhibitors)

highly-maintained genes and proteins such as BMAL1 and CLOCK, the key molecular determinants of circadian rhythms. These proteins bind together, forming a heterodimer with nuclear transcription activity that recognizes E-box elements throughout the genome, leading the transcription of clock-related genes. Several local and systemic retroaction processes contribute in establishing the 24-hour intrinsic period of the circadian rhythm.

Numerous studies have shown that inflammatory pain can be subjected to circadian rhythm-based variations in intensity, evidenced using specific markers such as cytokines [17], immunocytes [16], hormones [18], or the modification of biorhythm *clock* gene expression [19]. More recently, similar variations were also observed in neuropathic pain conditions such as peripheral diabetic neuropathy or post-herpetic neuralgia [20].

With regards to chronic orofacial pain, the only studies pertaining to such circadian variations were undertaking in patients with burning mouth syndrome (BMS), where a circadian variation in pain intensity was observed throughout the day [21]. To the best of our knowledge, no such study has been undertaken on PTTN so far.

This study thus aimed to explore the time course of pain intensity throughout the day in patients suffering from PTTN.

Materials and methods

A pilot prospective observational, non-interventional, study was conducted in the Dental Medicine department of the Groupe Hospitalier Pitié-Salpêtrière (GHPS) in Paris, between January and December 2019. Study participants were patients consulting in the tertiary orofacial pain clinic and fulfilling the inclusion criteria (Table I). The study design was approved by an internal department board and by an Institutional Review Board (CPP 2017-002353-11). The study was conducted in strict adherence with the Helsinki declaration principles. All included patients received oral and written information and all signed an informed consent before the start of the study. Patient anonymity was enforced throughout the study.

Study aims and outcomes

In adherence with relevant recommendations of chronic pain assessment (IMMPACT [22]), this study evaluated pain intensity, psychosocial status and quality of life of included participants.

The *primary aim* of this study was to evaluate the daily diurnal pain intensity in patients suffering from PTTN, accordingly to a previously described methodology (Braud *et al.* [21]). Primary study outcome was thus pain intensity evaluated using an 11-point Numerical Rating Scale (NRS) from 0 = no pain to 10 = worst imaginable pain. Patients were instructed to assess their pain levels every hour for 8 consecutive days, from waking to bedtime. As pain levels can be modified during food intake, timing of measurement was modified before or after meals, so as not to interfere with the measure [21].

Secondary aims of the study focused on evaluating oral health-related quality of life and anxio-depressive state. Oral health-related quality of life was assessed using the General Oral Health Assessment Index (GOHAI) [23]. Such questionnaire is comprised of 12 items, graduated between 1 and 5. Overall score (GOHAI-Add) can be obtained by summing the scores for each item, thus varying between 0 and 60. Low scores (between 12 and 50) indicate a low oral quality of life; scores between 51 and 56 are moderate scores; scores between 57 and 60 are high scores, suggestive of good oral quality of life. Emotional status was assessed using the HADS (Hospital Anxiety and Depression Scale) questionnaire which focuses specifically on anxiety and depression [24]. HADS is comprised of two questionnaires: HAD-A evaluating anxiety and HAD-D evaluating depression: a score lower than 7 indicates lack of symptomatology; a score between 8 and 10 is indicative of suspected symptomatology and a score higher than 10 is indicative of certain symptomatology.

Inclusion protocol

First consultation included medical anamnesis, locoregional clinical examination, exo and endobuccal examination, followed by an orthopantomogram. When required, other exams were requested: blood tests, tridimensional imaging (CBCT) focused on the injured area and/or brain MRI. Inclusion criteria are listed in Table I, and were in adherence with the diagnostic criteria of the International Headache Society (IHS) [1]. At the end of the consultation, a questionnaire for self-evaluation of pain intensity was given to the patients, to be completed every hour for 8 consecutive days, in addition to GOHAI and HADS questionnaires.

Statistical analyses

Descriptive statistics were used in the present study. The variable "pain intensity" was assessed throughout the day using a non-parametric Friedman test on paired data, followed by a post-hoc multiple comparisons Dunn test. Significance level was set at $p < 0.05$.

Results

The patient cohort was comprised of 11, middle-aged (mean age 59.1 ± 14 years old) female patients suffering from PTTN. Two patients did not adequately complete their GOHAI and HADS questionnaires, and thus such incomplete data was excluded from study results.

Pain intensity

In 100% of cases, pain intensity followed a circadian rhythm, weaker during the morning hours and increasing through the day, peaking before bedtime. Such pain evolution profile was globally similar during the whole study period (8 days). Neither nocturnal pain nor sleep interference was reported. Mean pain intensity was 3.6 ± 0.99. Within the whole cohort, mean pain levels slowly and significantly ($p < 0.0001$) increased throughout the day, from 1.8 ± 1.3 to 4.6 ± 2.3, in a linear fashion (Fig. 1). Differences in pain levels, as compared to 8 AM values, were statistically different starting from 5 PM and later. The curve of pain scores as a function of time was as follows: $f(x) = 0.18x + 1.89$.

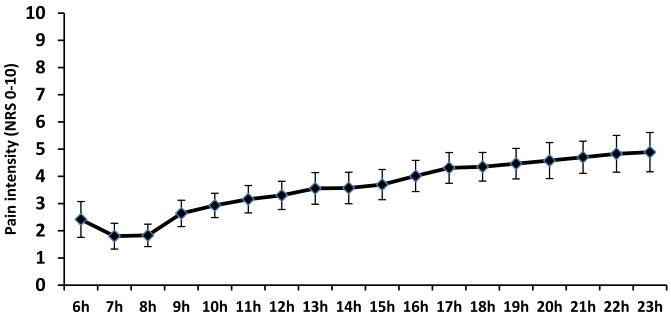

Fig. 1. Evolution of pain intensity of patients suffering from PTTN ($n = 11$). Mean pain intensity (M ± SEM) auto-evaluated using a numerical rating scale (NRS) from 0 to 10 is reported every hour during waking period. The curve represents the mean value of all patients measured over 8 consecutive days. Noteworthy is the quasi-linear increase in pain intensity throughout the day.

Psychometric data

Mean HAD-A and HAD-D scores were 9.6 ± 3.0 and 5.8 ± 3.8 respectively. Anxiety and depression scores per pain intensity are reported in Figures 2A and 2B respectively. Pearson correlation coefficients were 0.069 and 0.0116 for anxiety and depression respectively, *i.e.* a weak correlation. The mean GOHAI score of the study cohort was 34 ± 6.7.

Discussion

The main result that can be drawn from this pilot study is a linear, circadian, increase in self-reported pain intensity throughout the day, in patients suffering from PTTN. Pain intensity increased slowly and significantly from morning (NRS = 1.8 ± 1.3) to evening (NRS = 4.6 ± 2.3) ($p < 0.0001$). These results confirm the validity of our methodology, as previously implemented in the study by Braud *et al.* 2013 [21], allowing the assessment of precise variations during the diurnal part of the nycthemeron.

Time course of pain in PTTN

There is scarce data focusing on the time course of neuropathic pain. To the best of our knowledge, only one clinical study retrospectively analyzed the chronobiological aspects of neuropathic pain [25]. The study authors documented a variation in pain intensity within a cohort of 55 patients suffering from painful diabetic neuropathy and 30 patients suffering from post-herpetic neuralgia, said variation being independent of administered treatments (gabapentine

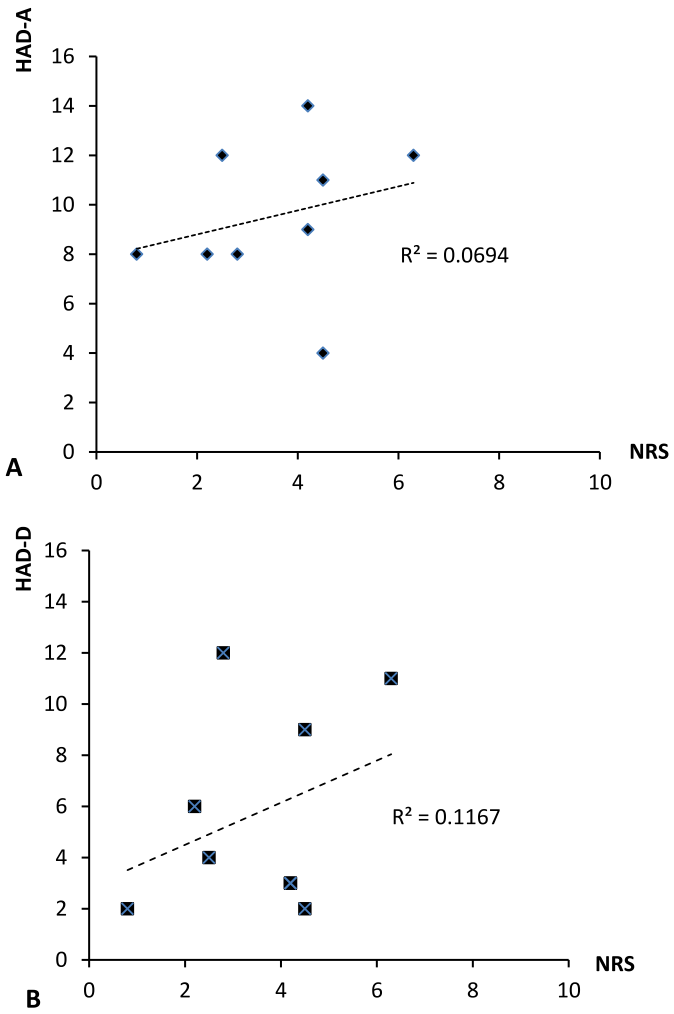

Fig. 2. HADS scores as a function of pain intensity in patients with PTTN ($n = 9$). (A) Anxiety scores (HAD-A). (B) Depression scores (HAD-D). Pearson's correlation coefficients suggest a weak correlation between HADS and NRS scores. NRS = Numerical Rating Scale (0–10); HADS = Hospital Anxiety and Depression Scale: scores between 7 and 10 suggest probable anxiety/depression, over 10 certain anxiety/depression.

and/or morphine). Our results suggest a similar circadian pattern of pain intensity increase throughout the day, although more precisely (their study only focusing on three timepoints: 8 AM, 4 PM and 8 PM). It should be noted that our study is the first to document such circadian variations in pain intensity in the context of neuropathic orofacial pain.

It is also noteworthy that circadian increase in pain intensity observed in the present study is similar to that observed in patients suffering from BMS in the study by Braud *et al.* 2013 (with differences in slope: 0.18 *vs.* 0.21) [21]. Furthermore, mean pain intensity was also similar: 3.6 ± 0.99 (PPTN) *vs.* 3.9 ± 0.3 (BMS). Such observations give further credence to the idea that pain in BMS resembles that of other neuropathic pain conditions [26].

Several explanations have been posited to account for the circadian variation of neuropathic pain, based on data from animal studies [15,27]. For instance, endogenous opioids, essential players in the control of pain, are subject to circadian rhythm modulations [28]: indeed, beta-endorphin levels are higher during the morning than in the evening [29]. They could thus be implicated in the observed time course. Another explanation can be posited, implicating the neuroglial system, activated following tissue injury. For instance, peripheral nerve lesions lead to a well-known increased in pro-inflammatory mediators, cytokines and chemokines, but also induce astrocytic and microglial activation and immunocyte recruitment [30]. These elements, implicated in the development of neuropathic pain, are also under circadian rhythm regulation [16].

Psychosocial impact of PTTN

The second main finding from this pilot study pertains to the impact of PTTN on oral health-related quality of life and function. Our results suggest that PTTN patients have low oral quality of life (mean GOHAI score = 34) and high scores of anxiety/depression (mean score of 9.6 and 5.8 respectively). Such results are in adherence with those of Renton's group that previously documented both quantitatively and qualitatively using a systematic psychometric panel (PHQ9, OHIP-14, PSEQ, GAD-7, etc.) the impact of neuropathic pain on psychosocial status and oral health-related quality of life [31,32]. They aptly underline the importance of multidisciplinary management of PTTN, with a specific focus on psychological therapies, despite current limited evidence of efficacy of such treatment options [33].

Study limits

This pilot study was designed to evaluate the feasibility and pertinence of larger observational studies. As such, only a limited number of patients were included, thus mitigating the conclusions that can be drawn from our results.

Conclusion

Results from the present pilot study suggest a circadian variation in pain intensity throughout the day in patients suffering from PTTN, thus advocating for more personalized pharmacological treatment at specific time points during the day.

Conflicts of interests: The authors declare that they have no conflicts of interest in relation to the publication of this article.

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