The enigma of the interconnection of trigeminal pain and cranial autonomic symptoms

Arne May¹ and Peter Goadsby²

In this issue of *Cephalalgia*, two papers by Dr Benoliel and colleagues highlight the clinical profile of patients with trigeminal neuralgia (TN) and make two main observations: The electric-like stabbing pain attacks can be distinguished in a shorter and longer version (1) and longer attacks are a negative prognostic factor for treatment (2). This is remarkable for two reasons: It allows us to perhaps stratify patients before starting medical treatment, and secondly, because the authors also focused on other clinical signs including the phenomenon of cranial autonomic symptoms, it touches on the issue of the differentiation between TN of the ophthalmic division and short-lasting trigeminal-autonomic headaches, namely short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) (3–5).

In the first manuscript (1), the authors investigated 81 patients with the diagnosis of TN following the International Headache Society’s published classification (6) and focused on clinical features such as autonomic signs, persistent background pain, attack duration and reports of pain-related awakening. They found that quite a substantial subgroup had rather long attacks, and when dividing the cohort into groups with short attacks (≤ 2 minutes, n = 61) and long attacks (> 2 minutes, n = 20), the short (duration) attack group fit most of the criteria for classical trigeminal neuralgia (CTN) while the long attack group did not. The authors’ use of the International Classification of Headache Disorders (ICHD) illustrates a fundamental complexity reminiscent of the entire diagnostic system: In the absence of biological markers, phenotype drives diagnosis; thus the diagnostic categories used may be called into question absent other markers. Moreover, as the authors mention in the Methods, atypical symptomatology was permitted to facilitate the study. A substantial confounding issue then becomes whether this was a study of TN or of a mixture of syndromes. A further substantial concern regarding cranial autonomic symptoms is the issue of whether it is their presence or prominence that is important. While both groups did not differ in pain severity, quality and location, the frequency of persistent background pain was significantly higher in the long (70%) compared to the short attack group (39%). The presence of persistence may be no more than a by-product of attack length, i.e. with longer attacks central sensitizing or neuropathic mechanisms may be more likely to be activated. Notably, there were no significant differences in the frequency of autonomic signs between both cohorts (2).

Building on these findings, the authors then enrolled 81 patients prospectively and stratified them regarding attack duration. All patients were treated using standardized pharmacotherapeutic protocols and a treatment outcome, with a ≥ 50% reduction was considered significant. Clinical improvement was significantly more frequent in the short (74%) than in the long attack group (50%). Additionally, in the short attack group, patients with a longer disease duration and the presence of autonomic signs had a significantly poorer treatment response than patients with a shorter disease duration and no autonomic signs (2).

Should these findings be replicated, they are certainly highly interesting for clinicians seeking a way to at least in part predict whether a medical treatment may be useful and how high or low the threshold for neuromodulatory treatments, such as thermocoagulation, should be in a particular patient. It also sheds light on the disease as such and allows us to perhaps clinically distinguish these patients better. Are patients

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¹Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Germany
²NIHR-Wellcome Trust King’s Clinical Research Facility, Kings College London, UK

Corresponding author:
Arne May, Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, Martinistr. 52, D-22046 Hamburg, Germany.
Email: a.may@uke.de
with a longer attack duration just a subgroup of TN or are we looking at a different disease altogether? A further layer of complexity is whether inter-paroxysmal pain is a manifestation of another biology; the authors of this editorial have the clinical impression that inter-paroxysmal pain is due to migraine biology in the patient. Although the presence of autonomic symptoms did not differ significantly between the longer and the shorter attack type, the immediate question is the demarcation to other stabbing and short-lasting headache syndromes such as SUNCT and SUNA; the fact that the presence of cranial autonomic symptoms predicted a poor therapeutic outcome to a treatment not typically useful in SUNCT/SUNA suggests these symptoms mark a particular biology. Both SUNCT and SUNA are short-lived extreme pain attacks, and both may well exhibit autonomic symptoms with the pain, and lastly both are treated with sodium-channel blockers (7). However, given that a classification cannot empirically be proven to be right or wrong (8), the authors have by definition looked into only TN and not into SUNA or SUNCT, i.e. they have per definition not investigated SUNA. Or have they?

The overlap between both syndromes is striking, and the authors certainly touched on the point that there may be a clinical and even pathogenic continuum between TN and SUNA. The clinical difference is marginal yet thought significant and comprises the fact that SUNCT and SUNA are usually triggerable without a refractory period. This is in contrast to TN, which usually has a refractory period after each attack. The difference in treatment response is also marginal, in that the first-line therapy for TN is carbamazepine, whereas SUNCT is usually treated using lamotrigine (9), which also works in TN. Both syndromes may be responsive to gabapentin (10), another antiepileptic. Regarding the pathophysiological concept of nerve-vessel contact in TN (11), several reports show that SUNCT patients either have it (10,11) or may even profit from a Janetta operation (12–14), although many patients do not profit from the procedure. The high percentage of remission after microvascular decompression would support the pathogenetic role of neurovascular compression (13), although without better quality-controlled studies, this is not a solved issue.

In summary, the clinical picture and therapy options seem to distinguish both syndromes but on closer inspection it is not so clear. Perhaps the distinction is clearer when looking at second- and third-division neuralgia, and this would lead to the suggestion that autonomic symptoms as part of the trigemino-autonomic reflex (15) are perhaps more likely in first-division neuralgia and particularly then the distinction between specific trigeminal autonomic cephalalgias and TN may be difficult. The enigma then remains why not all first-division head pain, but only some distinguished syndromes, regularly exhibit autonomic symptoms. In any case, any syndrome defined in the International Headache Society’s published classification (6) can be changed only if, by strictly applying the defined criteria, additional features of this syndrome come to light that were not evident when the classification was made and might thus be added to the classification (8). The findings by Haviv et al. and Benoliel et al. are certainly thought-provoking and point toward a possible continuum between TN and SUNT or SUNA, although one reading is the data illustrate two syndromes that have not been or cannot be well differentiated here. Moreover, these studies underline that a longer disease duration and the presence of cranial autonomic signs accompanying the pain attacks are negative prognostic indicators and now long attack duration is added as a further negative prognostic sign. This opens the door to stratifying these patients clinically and certainly new studies to better understanding these syndromes.

References

7. Cohen AS, Matharu MS and Goadsby PJ. Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) or cranial autonomic features (SUNA)—a prospective clinical study of SUNCT and SUNA. Brain 2006; 129: 2746–2760.


