Tic, Triggering, and Tearing: From CTN to SUNHA

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Premise.—Classical trigeminal neuralgia (CTN) and the short-lasting unilateral neuralgiform headache attacks (SUNHA) are clinically similar.

Problem.—The SUNHAs include short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA). Shared clinical signs with CTN include severe, unilateral trigeminal pain that is often triggered by innocuous stimuli and accompanied by a dull persistent background pain. Recent reports on trigeminal neuralgia cases with atypical features such as autonomic signs and prolonged attack duration further blur the clinical distinction between CTN and SUNHAs.

Potential solutions.—Are the similarities greater than their differences? If so, this may reflect a spectrum of disease ranging from typical CTN attacks to typical SUNHAs with a mixed phenotype in the middle. In this review they will summarize the overlap between these entities and contrast the pathophysiology and treatment approach.

Key words: CTN, SUNHA, trigeminal neuralgia

INTRODUCTION: THE OVERLAP BETWEEN CTN AND SUNHA

Classical trigeminal neuralgia (CTN) is a paroxysmal, short-lasting (<2 min), unilateral, facial pain of excruciating intensity.[1] Quality is overwhelmingly described as electric-like, shooting, stabbing or sharp (Table 1).[1] Pain paroxysms are typically precipitated by innocuous stimuli to the affected side of the face (also known as triggering), but are often spontaneous.[1] CTN is subdivided into purely paroxysmal and that with persistent background facial pain.[1] This is based on consistent findings that up to one half of CTN patients describe the typical paroxysmal attacks of short sharp pain superimposed on a dull background pain of varying duration.[2] Previously referred to in the literature as "atypical" or type 2,[3,4] the criteria for diagnosis of CTN with persistent background facial pain include those for CTN in addition to "persistent facial pain of moderate intensity in the affected area" (Table 1).

Short-lasting unilateral neuralgiform headache attacks (SUNHA) are considered primary headache disorders and are included among the trigeminal autonomic cephalalgias (TACs). TACs are unilateral craniofacial pain syndromes characterized by prominent ipsilateral cranial parasympathetic features.[1] The SUNHAs include short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA). The criteria for diagnosis of SUNCT and SUNA are presented in Table 2. SUNCT is diagnosed if both conjunctival injection and lacrimation occur ipsilateral to the pain, while SUNA is diagnosed if only one or neither of conjunctival injection and lacrimation occurs. There are no data on whether SUNCT and SUNA are discrete entities or variants of the same disorder; however, the classification committee suggested that SUNCT may be a subset of SUNA[1] and grouped these together.

The clinical similarities between CTN and SUNHAs are clear. However, following the first description of SUNCT in 1989,[5] the justification for a separate classification to CTN was stated as "In several respects (unilaterality, triggering, brevity, and frequency of paroxysms), SUNCT shows similarity to trigeminal neuralgia. SUNCT seems to differ clearly from trigeminal neuralgia in other respects: sex distribution (SUNCT patients are often males), pain localization (SUNCT patients have the pain in the ocular area), the carbamazepine effect, presence of conjunctival injection, lacrimation, etc. SUNCT may accordingly altogether seem to be distinct from trigeminal neuralgia."[6] It was suggested that cases of CTN with tearing are probably cases of misdiagnosed SUNCT syndrome,[6-8] and this disagreement has been common.[9]

However, as we shall show in this review, the more recently documented spectra of clinical presentations of CTN often overlap with SUNHAs creating a challenging differential diagnosis and raising questions regarding their separate classification. The International Classification of Headache Disorders 3rd Edition (ICHD-3) clearly classifies SUNHAs and CTN separately based on ostensibly individual and specific clinical features.[1] SUNHAs are classified as a TAC,[1] based on the

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Headache

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Table 1.—Diagnostic Criteria for Classical Trigeminal Neuralgia (With Permission From the International Headache Society [IHS] 2013)

Diagnostic criteria for Classical trigeminal neuralgia (CTN)

A. At least three attacks of unilateral facial pain fulfilling criteria B and C
B. Occurring in one or more divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution
C. Pain has at least three of the following four characteristics:
1. Recurring in paroxysmal attacks lasting from a fraction of a second to 2 minutes
2. Severe intensity
3. Electric shock-like, shooting, stabbing or sharp in quality
4. Precipitated by innocuous stimuli to the affected side of the face
D. No clinically evident neurological deficit
E. Not better accounted for by another ICHD-3 diagnosis

Diagnostic criteria for Classical trigeminal neuralgia, purely paroxysmal

A. Recurrent attacks of unilateral facial pain fulfilling criteria for 13.1.1 Classical trigeminal neuralgia
B. No persistent facial pain between attacks

Diagnostic criteria for Classical trigeminal neuralgia with concomitant persistent facial pain

A. Recurrent attacks of unilateral facial pain fulfilling criteria for 13.1.1 Classical trigeminal neuralgia
B. Persistent facial pain of moderate intensity in the affected area

clinical phenotype of a unilateral headache involving autonomic activation[10] and on neuroimaging studies showing patterns similar to other TACs.[11] Yet, although TACs are distinctive clinical syndromes, misdiagnosis seems relatively common, with trigeminal neuralgia appearing amongst the most frequent.[12-14] The overlap in the clinical profile, together with descriptions of possible "transformation" between SUNHA and CTN,[15-17] challenge the current clinical classification.

CTN and SUNHA as a Spectrum

A possible explanation to this somewhat complex diagnostic challenge is to view CTN and SUNHA as part of a spectrum.[18] SUNHA and CTN may be attributable to a unifying pathophysiological model characterized by different degrees of interaction between peripheral and central mechanisms, namely focal demyelination of the trigeminal sensory root and posterior hypothalamic dysfunction.[18]

The number and type of clinical phenomena in CTN and SUNHA may be dependent on disease duration and other comorbid factors, which determine the patient's profile and prognosis. At one end of the spectrum are patients with short paroxysmal attacks, moderate pain, and short disease duration, with few clinical phenomena associated with central sensitization (eg, no background pain) or no comorbidity of the hypothalamus (minimal parasympathetic dysfunction, no cranial autonomic signs [CAS], no sleep disturbances) and a good response to treatment.[19,20] Clearly the pain, sleep, and hypothalamic relations are very complex but beyond the scope of this review.[21] In the middle are patients with longer, severe attacks, longer disease duration, increased reports of waking from sleep, background pain, and CAS. Finally, at the other end of the spectrum are patients with severe pain, long paroxysms of pain, and longer disease duration, presenting with many clinical phenomena associated with central sensitization and parasympathetic dysfunction, such as constant background pain, intense autonomic activation, a high frequency of waking, and poor response to treatment.[19,20]

This article highlights the overlap of individual signs and symptoms, which we routinely use for diagnosis, in CTN and SUNHA. We will examine the current classifications of CTN and SUNHA according to the ICHD-3, which may account for some of the confusion in patient diagnoses.

For a summary on the differences between CTN and SUNHAs, please see Table 3.

Prevalence, Age of Onset, and Sex Predilection

The annual incidence of CTN is 4-13 per 100,000 people,[22,23] and it affects women more than men. Peak incidence

Table 2.—Diagnostic Criteria for SUNHAs (With Permission From the International Headache Society [IHS] 2013)

Diagnostic criteria for short-lasting unilateral neuralgiform headache attacks (SUNHA)

A. At least 20 attacks fulfilling criteria B-D
B. Moderate or severe unilateral head pain, with orbital, supraorbital, temporal and/or other trigeminal distribution, lasting for 1-600 seconds and occurring as single stabs, a series of stabs, or in a sawtooth pattern
C. At least one of the following cranial autonomic symptoms or signs, ipsilateral to the pain:
1. Conjunctival injection and/or lacrimation
2. Nasal congestion and/or rhinorrhea
3. Eyelid edema
4. Forehead and facial sweating
5. Forehead and facial flushing
6. Sensation of fullness in the ear
7. Miosis and/or ptosis
D. Attacks have a frequency of at least one a day for more than half of the time when the disorder is active
E. Not better accounted for by another ICHD-3 diagnosis

Diagnostic criteria for SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing)

A. Attacks fulfilling criteria for short-lasting unilateral neuralgiform headache attacks
B. Both of conjunctival injection and lacrimation (tearing)

Diagnostic criteria for SUNA (short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms)

A. Attacks fulfilling criteria for short-lasting unilateral neuralgiform headache attacks

Table 3.—Comparison of Features Between CTN and SUNHA

Parameter	Classical Trigeminal Neuralgia	Short-Lasting Unilateral Neuralgiform Headache Attacks
Classification of headache disorders according to the IHS 2013	Painful cranial neuropathies and other facial pains	Trigeminal autonomic cephalgias (TACs)
Prevalence	Annual incidence 4-13 per 100,000 people	Annual incidence 1.2 per 100,000 and the prevalence is 6.6 per 100,000
Mean onset	50-60 years and increases gradually with age	About 50 years
Sex distribution	Female predominance	*SUNCT patients are often males (1.5:1) *SUNA may be more common in females (1:2)
Laterality	*Unilateral *Bilateral cases in 1%-5% (usually sequential rather than concomitant)	*Unilateral *Bilateral cases are rare
Location	Occurring in one or more divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution: V1: 2% V2 or V3: 16%-18% V2 and V3: 35% All three branches: 14%	Located in orbital, supra-orbital, temporal and/or other trigeminal distribution: SUNCT: V1: 67% V2: 33% V3: none SUNA V1 and V2: 56% V3: 33%
Progressive involvement of lower trigeminal branches in V1 patients	Yes	No
Radiation beyond the trigeminal distribution	No	Yes, such as the back of the head (28% of SUNCT and 22% of SUNA)
Pain quality	Paroxysmal, shooting, sharp, piercing, stabbing, or electrical in nature	Burning, stabbing, and sometimes electric
Pain severity	*Severe *In patients with background pain the constant pain is of moderate intensity	*SUNCT: moderate to severe *SUNA: may be slightly less severe
Remissions	May last from weeks to years	May last for several months
Duration	A fraction of a second to 2 minutes	1-600 seconds
Frequency	–	*At least one a day *More than half of the time in active disorder
Pattern	*CTN: short attacks of pain *CTN with background: longer-duration patterns	Occurring as single stabs, a series of stabs, or in a sawtooth pattern
Autonomic signs	*Mild autonomic symptoms such as lacrimation and/or redness of the eye may be present *AS are noted in the comments and are not part of the diagnostic criteria	*By definition SUNHAs are accompanied by AS SUNCT: both of conjunctival injection and lacrimation SUNA: only one or neither of conjunctival injection and lacrimation
Triggering	Triggering is part of the definition: pain is precipitated by innocuous stimuli to the affected side of the face, such as: Talking (76%) Chewing (74%) Touch (65%) Temperature (cold 48%, heat 1%) Wind and shaving No clear trigger (40%-50%)	*SUNCT and SUNA are usually triggerable (80% in SUNCT, lower incidence in SUNA) *Triggering is noted in the comments and is not part of the diagnostic criteria
Refractory period	Yes	No
Sensory deficits	By definition no clinically evident neurological deficit (however, were reported in around 30% of series of CTN patients)	None
Background Pain	*Dull, throbbing and burning of moderate intensity *Present in 35%-49% of patients	Present in 50% of patients
Sleep	Pain related awakenings: 30%	Pain related awakenings are rare
Neuroimaging studies—neurovascular compression (NVC)	*CTN (89% symptomatic and 78% asymptomatic side) *Severe CTN (53% symptomatic and 13% asymptomatic side) *Bilateral CTN (<50%) *Recurrence CTN after initially successful MVD (0%) *Age-matched CTN-free controls (17%)	*SUNCT/SUNA (17%) *May respond to MVD in up to 75% of cases *Neuroimaging studies patterns are similar to other TACs
The carbamazepine effect	*70%-98% respond initially *Older data suggested increasing resistance while newer data suggest otherwise *Short attack duration (74%); long attack group (50%) *CTN with concomitant persistent facial pain and/or AS also exhibits poor response	*Resistance to a wide range of drugs from their onset (untested in prospective trials) *One third of previously misdiagnosed SUNCT cases respond partially to carbamazepine *Lamotrigine is considered the treatment of choice in SUNHA
Prognosis	Poor *Some report increased attack frequency and severity *There may be a decline in the response to carbamazepine in some patients *Reduced surgical prognosis in CTN lasting >7 years	We have no knowledge of reports regarding similar time-related changes in SUNHAs' response to treatment

of CTN begins at 50-60 years and increases gradually with age. Female predominance may therefore be related to the increased longevity of women compared with men.

SUNHA and CTN seem to have similar epidemiological features. SUNA may be more common in females (1:2), but SUNCT seems slightly more prevalent in males (1.5:1).[10,24,25] The overall estimated annual incidence of SUNHAs is 1.2 per 100,000, and the prevalence is 6.6 per 100,000.[26] Cases of all ages have been reported, from childhood to old age, with a mean onset of about 50 years, similar to CTN.[24,27]

Clearly, we are dealing with the differential diagnosis of two rare diseases. This makes studying and comparing them extremely difficult. Specifically, SUNHAs are very rare, but it is possible that the clinical similarities with CTN and even cluster headache (CH), lead to the misdiagnosis of many cases.[24] SUNHA may therefore be more common than estimates based on the sparse case reports.

SUNCT occurring in siblings or "familial SUNCT" has been reported[28] and raises the possibility that SUNCT together with migraine, CH, and possibly other TACs will eventually be considered to be of genetic predisposition. Similarly rare familial CTN cases have been reported.[29,30] Moreover, CTN has recently been linked to polymorphisms in the serotonin transporter gene.[31]

Location

CTN is considered a unilateral facial pain syndrome.[1] However, bilateral cases have been reported in 1%-5% of cases, but one side usually precedes the onset of pain on the contralateral side by years.[2,32,33] In the presence of bilateral symptoms as well as trigeminal sensory loss, especially in patients younger than 40 years, the presence of a space-occupying lesion or multiple sclerosis is suspect. Reviews of case series suggest that the right side is involved more often; however, this is inconsistent and as no correlation has been found with age, sex, or handedness, the clinical significance is doubtful. Although the location, intensity, and triggers of CTN vary across patients, they are highly stereotyped within individual CTN patients; that is, each attack is similar in location, duration, and intensity.

Pain location is usually described according to the major branches of the trigeminal nerve and pain radiation is within the dermatome of origin. In 16%-18% of patients, the singly affected nerve will be the maxillary (V2) or the mandibular branch (V3), whilst the ophthalmic (V1) is affected singly in only about 2% of cases. Most commonly, the V2 and V3 branches are affected together (35%), and all three branches are involved in 14% of patients.

Location seems a driving force in guiding patients on whom to consult for their pain. Since the jaws are involved in most CTN patients, this explains why they so often seek help from dentists. Indeed, in our CTN cohorts,[7,20,34,35] there are few patients with pain in the V1 trigeminal division; patients choose their medical specialist based on pain location. Cases with tooth/jaw pain (V2 and V3 divisions) tend to choose dental practitioners, whilst the presence of eye pain may guide them to neurologists and ophthalmologists. Similarly, pain over the malar (sinus) region may lead patients to consult an otolaryngologist. There is thus selection bias in studies composed of convenience cohorts from different specialty clinics.

In SUNHAs, pain is unilateral with no obvious side predilection and rarely spreads across the midline.[24] There may be attacks that change sides in a minority of patients, and, rarely, bilateral pain.[10] Previously considered to be exclusively located in the temporal, auricular, and occipital regions,[24] it is now recognized that pain may occur throughout the trigeminal system.[10] Primary location in SUNHAs is therefore similar to that seen in CTN. However, in contrast to CTN, where pain is exclusive to the trigeminal dermatomes, in SUNHAs, pain can occur outside the trigeminal dermatomes, such as the back of the head (28% of SUNCT and 22% of SUNA).[10,36]

In the largest SUNCT and SUNA series published, 67% of SUNCT patients complained of pain in V1, 33% in V2, and none in V3, in contrast to 56% of SUNA patients who reported the maximal intensity of the pain in V1 and V2, and 33% in V3, suggesting a continuum with CTN in which the majority of the patients report attacks in V2, V3, or both.[10,18,37] Since CAS are not part of the diagnostic criteria of CTN, but are part of the comments, cases presenting with V1 pain distribution and lacrimation will be most likely diagnosed as SUNCT/SUNA and not as CTN. Moreover, while both of conjunctival injection and lacrimation are mandatory for the diagnosis of SUNCT, other flexible combinations of CAS according to the location of pain are part of the comments and are not mandatory. Therefore, a patient presenting with pain in the V2 and V3 distribution and mild CAS may have these overlooked and will be most likely diagnosed as CTN. It is thus probable that V2 and V3 SUNCT/SUNA are under reported. Recently, Lambru and Matharu suggested that when SUNHA occurs in the maxillary and mandibular dermatomes, tearing and conjunctival injection may be rare or absent.[38] With this in mind, it is possible that SUNHA patients with little tearing or conjunctival injection are often diagnosed as CTN. A question arises as to whether reported series of patients termed "CTN with tearing" are indeed CTN, or are they really SUNA?

Interestingly, patients with V1 CTN showed progressive involvement of lower trigeminal branches in long-term follow-up.[39] Similar late-phase co-involvement of V2 and V3 has not been reported in SUNCT series,[36,40] but may be an interesting research focus. Is the spread of pain to trigeminal and extra-trigeminal sites in SUNHAs a specific feature or part of the spectrum reflecting central sensitization with disease

progression? Unfortunately, we do not have sufficient data to address this.

Pain Quality and Severity

Pain in CTN is most often described as paroxysmal, shooting, sharp, piercing, stabbing, or electrical in nature (70%-95%).[41,42] Pain severity in CTN is extreme; ratings of 9-10 on a 10-cm visual analogue scale (VAS).[43,44] CTN patients report characteristic, paroxysmal attacks of pain, which are typically severe, although some patient report moderate pain. CTN patient with constant background pain usually report the persistent pain to be of moderate intensity.[3,42]

SUNCT is considered a moderate to severe pain syndrome,[10,24,26] and SUNA may be slightly less severe.[10] It is rarely pulsatile, but rather is usually burning, stabbing, and sometimes electric.[10,25,45] Nevertheless, Cohen et al reported that 84% of their 43 SUNCT patients rated their pain as 10 of 10 on an 11 point visual analog scale (VAS) scale, and 66% of SUNA patients rated their pain as either VAS 9 or 10.[10] These are more severe than previously appreciated for the SUNHAs and very reminiscent of pain intensity in CTN.

Disease Duration

Long-term follow-up of CTN patients reveals that there are well defined periods of pain attacks variably followed by periods of remission that may last from weeks to years. Similarly, remissions have been also observed in SUNCT and may last for several months.[46]

CTN has been considered a progressive disease with a poor prognosis,[47] with about 90% reporting increased attack frequency and severity.[43,48] The duration of pain attacks can change over time and become more prolonged as well as severe.[20] Historically, the response to carbamazepine is cited around 70% initially; by 5-16 years the response rate is around 20%, with 44% of patients requiring drug combinations or alternative medication.[49] Long-term follow-up of oxcarbazepine-treated CTN cases demonstrated a high failure rate necessitating surgery.[48] However, a 2014 data study called this into question. In this series of patients, 98% reported initial improvement with carbamazepine (mean 600 mg, range 200-1200) and 94% with oxcarbazepine (mean 1200 mg, range 600-1800).[50] Over the period of their study, 3 of 95 patients developed resistance to CBZ and 2 of 83 to oxcarbazepine. In the same series, only 3% reported a worsened intensity and 2% increased duration of paroxysms. The conflict between the findings cannot be resolved at this point. It is quite possible, as previously stated, that each reported cohort from different types of specialty centers is different from others, resulting in unanticipated bias, with patient selection leading to different outcomes.

Notwithstanding, some type of disease progression in CTN is supported by the finding that microvascular decompression (MVD) has a significantly reduced prognosis in CTN lasting greater than 7 years.[51] This is in line with a hypothesis the authors previously presented,[19] whereby longstanding disease leads to a more complex patient profile with poor response to treatment. We have no knowledge of reports regarding similar time-related changes in SUNHAs' response to treatment.

Attack Duration

In CTN, individual attacks have rapid onset and peak, and then subside, lasting overall from 10 seconds up to 2 minutes.[1,52] In SUNHA, attacks also begin rapidly and end abruptly.[45] A SUNHA attack lasts from 1 to 600 seconds, with a mean duration of about 1 minute,[10] but longer lasting attacks of even 2-3 hours have been reported.[10,53] Frequency ranges from 2 to 600 daily, with an average of 59 per day; many patients have such frequent attacks they may be unable to quantify them.[10] A "cluster-like" pattern has been reported with active and inactive episodes but is variably present. Rarely "SUNCT status" occurs, which consists of pain lasting for the better part of the day for 1-3 days.

Characteristic patterns of attacks in SUNHAs are now recognized; single attacks may last a bit longer with a "plateau-like" pattern,[54] Shorter-lasting attacks in rapid succession or "repetitive" attacks may occur. The "sawtooth-like" pattern consists of consecutive spike-like paroxysms without reaching a pain-free baseline. A mixture of short attacks on top of the typical plateau pattern termed "plateau-like plus exacerbations" has also been described.[10,26,45] The recognition of the varying pain patterns in SUNHA is significant, as the short attacks of pain could be mistaken for CTN and the longer-duration patterns of stab groups and sawtooth could be mistaken for CTN with background pain, CH, or paroxysmal hemicranias (PH).[36]

Although according to ICHD-3 criteria, CTN duration has a cutoff at 2 minutes,[1] it is important to note that attack duration in CTN has not been thoroughly validated, and we continue to rely on patient reports. This reliance has significant potential for error but is still customary.[2,32,33]

Patients with attacks longer than 2 minutes challenge the diagnosis of CTN; is it possible that CTN may occur with attacks of greater than 2 minutes? In two series of CTN patients, some patients reported attacks of 2-3 minutes[55] or longer.[20] CTN patients may report a dull aching pain that continues for a considerable amount of time after the paroxysm.[56] It is possible that patients with attacks greater than 2 minutes are reporting both of these types of pain, the paroxysm and the "after-pain" as one. Additionally, some CTN patients report multiple overlapping attacks that may feel as one longer attack. This would, however, be an unlikely occurrence in the presence of a refractory period.

It is more likely that the CTN patients with long attack duration may form part of a spectrum with SUNCT and SUNA. When examining individual sign and symptom

profiles in our CTN patients with long attack duration, some patients demonstrated a phenotype similar to that of SUNA.[20] For example, patients with long attacks had more frequent CAS (40%) than in patients with short attack duration (21%).[20] Examining individual patients, 11 had significantly prolonged attacks but no CAS. Under current thinking, these patients would likely not be diagnosed as SUNA or SUNCT, and their presentation supports the proposition that longer attack durations are indeed part of the CTN spectrum.[38] Moreover, within this last group of patients, eight of them demonstrated an identifiable trigger area and refractory period in the presence of paroxysms lasting significantly longer than 2 minutes.[10,20]

In the same CTN cohort, we observed that constant background pain was present in most patients reporting long attack duration.[20] The association between longer attack duration and background pain may be attributed to the "after-pain," which may continue to increase in duration until it becomes a constant background pain. Indeed, the duration of pain attacks can change over time and become more prolonged as well as severe. However, DeStefano et al reported that only 2% of their patients developed increased duration of paroxysms and constant pain after 4.5-7 years during a study of the natural history of CTN.[50] Notwithstanding, in a previous study on CTN patients, we found a significant correlation between attack duration and disease duration.[55]

Therefore, based on the literature and the data presented, there seems to be an association between long disease duration, long attack duration, presence of background pain, and CAS. Clearly, a large prospective study on the natural history of CTN is needed to confirm this. The overlap of such cases in clinical phenotype between that expected of CTN and that of SUNHA is so significant as to make differential diagnosis difficult if not impossible.

Cranial Autonomic Signs (CAS)

By definition SUNHAs are accompanied by CAS. According to the ICHD-3, these may include ipsilateral: conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating and flushing, sensation of fullness in the ear, miosis, ptosis, and/or eyelid edema. SUNCT is diagnosed if both conjunctival injection and lacrimation occur ipsilateral to the pain, while SUNA is diagnosed if only one *or neither* of conjunctival injection and lacrimation occurs. In SUNCT there is marked ipsilateral conjunctival injection and lacrimation that appear rapidly with onset of pain.[24] Nasal stuffiness and rhinorrhea are common, whilst sweating may accompany attacks but is rare and often subclinical. CAS may appear regardless of the site of pain, which may occur in the maxillary or mandibular dermatomes.[10]

Experimentally, painful experimental stimuli in areas innervated by trigeminal nerve divisions V1 and V2 will cause ipsilateral lacrimation and nasal stuffiness or rhinorrhea.[57] These effects are largely considered secondary to initiation of a parasympathetic reflex via trigeminal nerve activation, the trigemino-parasympathetic reflex (TPR). In SUNCT/SUNA, the activation of trigemino-parasympathetic reflex also involves activation of the posterior hypothalamus.[58] The activation of a similar brain area was also seen in patients with CTN.[58] In TACs, parasympathetic signs have been postulated to occur secondary to activation of the TPR. Current thinking places the hypothalamus as a modulator of the TPR[59] and in terminating pain attacks,[60,61] so that hypothalamic dysfunction may act in a permissive role in both phenomena. However, no studies that we know of have examined this in CTN patients.

Characteristically CAS, such as lacrimation, are not considered part of the neuropathic pain phenotype. However, CAS in association with CTN may occur in up to two-thirds of patients[62] and were reported as long ago as 1914, when vasomotor and secretory signs were seen during paroxysms of pain.[63] The appearance of specific CAS, such as lacrimation in CTN is inconsistent. Reports suggest that lacrimation is present in over a quarter of CTN cases, regardless of the site of pain.[7,20,39,62,64] The sole presence of lacrimation in this type of CTN creates a clinical overlap with SUNA, but less so with SUNCT where there are two CAS. Other evidence of autonomic activity in CTN is found in reports of facial flushing (vasodilation), increased salivation, and swelling.[62,65] There seems to be a trend in the type of autonomic symptoms in CTN that vary according to pain location: V1 pain was associated with conjunctival injection, tearing, and ptosis; V2 pain was most often associated with facial swelling, and V3 pain was most often associated with excessive salivation.[62] The authors suggested that there is maximal parasympathetic activation in the region of the pain in CTN,[62] a type of segmental TPR. The appearance of CAS in CTN was related to disease duration in CTN[39] and correlated with longer attack duration[52] as well as with increasing pain severity and a poorer response to pharmacological therapy and surgical microvascular decompression.[62] In contrast, in SUNCT, autonomic phenomena were associated with relatively low pain levels, and were present from the very beginning.[39,62]

Altered autonomic function in CTN patients was demonstrated by Leonard et al in 2015.[66] In response to an experimental pain (cold pressor test), cardiac sympathetic activity was increased, while cardiac parasympathetic activity was decreased in CTN patients relative to controls. Moreover the exact relationship between CTN and autonomic dysfunction—causation or consequence—remained unclear.[66] To adequately study CTN patients with CAS and the way they interface with SUNHAs we may need a new subclassification of CTN with CAS. Indeed, the presence of CAS is an independent predictor of a poor response to pharmacological

therapy[19] as well as to microvacular decompression[62] giving this subclassification significant clinical relevance.

Sjaastad et al noted that autonomic phenomena in SUNCT are associated with relatively low pain levels, compared with CTN where autonomic features occur with increasingly severe pain.[39] Indeed, appearance of CAS in some headaches is variable and has been linked to pain severity with parasympathetic activation only occurring above a certain pain threshold.[62,67,68] If so, when CTN is particularly severe, trigeminal-autonomic activation may occur.

Triggering

The diagnostic criteria of CTN include the premise that pain may be precipitated by light, innocuous touch in trigger areas. A short gap between stimulation of a trigger area and pain onset may be observed and is termed ***latency***. Trigger areas in CTN are usually in the distribution of the affected trigeminal branch, particularly around the lips but may be extra-trigeminal,[43] multiple, and even change location. The triggering stimuli are innocuous and include talking (76%), chewing (74%), touch (65%), temperature (cold 48%, heat 1%), wind, and shaving.[43] However, CTN attacks are often spontaneous, and trigger areas are not always present or clinically identifiable; 40%-50% of CTN patients may not report a clear trigger.[20,42] Indeed, trigger-like areas may also be detected in about 9% of other orofacial pain syndromes.[42]

Pain in SUNCT/SUNA may be triggered by light mechanical stimuli in the areas innervated by the trigeminal nerve, chewing, tooth brushing, or wind[10,26] Trigger areas are common in SUNCT, occurring in 80% of patients;[26] however, there seems to be a lower incidence of triggers in SUNA than in SUNCT.[10,26] Triggering is not part of the ICHD-3 diagnostic criteria of SUNHA patients but is noted in the comments, and therefore cases presenting with triggering, in particular in V2 or V3 distribution will be most likely diagnosed as CTN. Interestingly, triggers in SUNCT/SUNA may not be responsive to local anesthetic blocks.[45] Extra-trigeminal triggers that precipitate pain attacks have also been reported in SUNHAs and include neck movements.[45]

Refractory Period

Triggering of pain in CTN is usually followed by a ***refractory period*** whose duration is related to the intensity of the CTN attack; during this time pain is impossible or extremely difficult to trigger. Refractory periods are frequently recognized in CTN[1] but rarer in SUNHAs,[10,26,69,70] although they have been reported.[71] A central disinhibition of the trigeminal nucleus caudalis may explain the lack of refractory periods in SUNCT/SUNA compared with CTN.[18]

Theoretically, when a refractory period is present one would not expect attacks to occur in rapid succession, as the first attack would inhibit the second attack, etc., as has been suggested in SUNHAs.[54] Thus, to date no similar patterns of successive attacks of SUNHAs have been reported in CTN. Is this a true differentiating feature or a reflection of the spectrum of disease?

Sensory Deficits

Sensory disturbances have been documented in CTN when employing sophisticated examination techniques.[72-74] Reflex and evoked potential studies also reveal nociceptive fiber dysfunction in CTN.[75] Importantly, following successful MVD, nerve conduction properties return to normal.[76] Clinically detectable sensory disturbances are rarer and inconsistently reported in CTN.[64,77] In a large series of CTN patients, sensory abnormalities were clinically detected in around 30% of their cases,[64] but in our 2016 series we found none.[20] Some suggest that clinically detected sensory abnormalities should form part of the spectrum of CTN.[77] This remains a contentious issue, and the ICHD-3 does not include these sensory changes in their criteria.

Clinical and neurophysiological studies in CTN therefore suggest the presence of nerve pathology. Rozen et al described a SUNCT patient who was found to have transient cutaneous allodynia during attacks but no sensory changes interictally.[78] Absence of sensory changes interictally suggests this is an expression of central sensitization to ongoing pain rather than an expression of nerve damage. The absence of trigeminal sensory pathway abnormalities in SUNHAs supports the view that it is not a neuropathic pain.[79]

Concomitant Persistent Facial Pain (Background Pain)

The new ICHD-3 sub-classification of CTN with concomitant persistent facial pain will aid in studying the pathophysiology, natural history, and treatment responses of this subgroup of patients. This classification is based on findings that 35%-49% of CTN patients describe two types of pain, paroxysmal attacks of short sharp pain superimposed on a dull background pain of varying duration.[2,20,35] Background pain may be described as dull, throbbing, and burning.[3] Background pain is of varying intensity with a mean VAS of 4.6.[2] Similarly, low-grade background (interictal) pain or local discomfort is common in SUNHAs (50%), even in the absence of medication overuse.[10,24] While the profile of CTN patients with persistent pain has been studied, suggesting a faulty pain modulation system or central sensitization,[80-82] we found no data on patients with SUNHA.

CTN patients with background pain seem to be a distinct subgroup of trigeminal neuralgia. In one recent series bilateral pain was significantly more common in CTN with background pain.[2] CTN patients with background pain are younger and more often females than in purely paroxysmal CTN.[2] Other features reported in CTN patients with persistent pain include longer attack duration of paroxysmal pain,[55] reduced prevalence,[2] or absence of a triggering mechanism,[42] waking from sleep,[35] CAS such as tearing,[7,39,62] less evidence for

neurovascular compression on MRI, and poor response to both pharmacologic and surgical treatments.[2,3,83-85] This profile is distinctly similar to that of the SUNHAs and supports the spectrum theory.

Sleep

Nocturnal attacks are common in TACs but were not considered typical of CTN. In our series,[20] pain related awakenings were reported by 29.5% of our CTN patients, similar to that previously reported.[35,86] In SUNHA a bimodal distribution of attacks occurring in the morning and late afternoon has been observed,[45] with less than 2% occurring at night.[45] We observed pain-related awakening in a significantly higher proportion of CTN patients with long attack duration.[20] Whether this is related to pain intensity or other factors remains unclear.

In TACs there is evidence of hypothalamic dysfunction that is purported to underlie associated sleep disorders.[59] Hypothalamic dysfunction may explain the reports of pain-related awakenings in SUNHA patients. However, awakenings in SUNHA are so rare as to make the connection tenuous at best.

Pathophysiology

The pathophysiology of most CTN cases has been considered to be secondary to compression of the trigeminal root at or near the dorsal root entry zone by an aberrant blood vessel.[3,76] This concept received wide support from imaging with correlated surgical findings,[87-89] and ultrastructural analysis of neuronal tissue.[90,91] These have confirmed neurovascular compression (NVC) in many patients with resultant clear histological damage to neurons and their myelin sheaths.

However, imaging studies in the 1970s suggested that NVC was present in healthy controls,[92] and cadaver studies in the 1990s showed that NVC was not ubiquitous to all CTN sufferers.[93] A 2015 imaging study in CTN patients found that NVC was prevalent both on the symptomatic and asymptomatic side (89% vs 78%), while *severe* NVC was highly prevalent on the symptomatic compared with the asymptomatic side (53% vs 13%).[94] These studies leave the role of NVC and the degree of NVC as factors in the causation of CTN unanswered.

In an elegant presentation, Burchiel outlined various lines of evidence that may question the NVC pathophysiologic concept and further blur the differences between CTN and SUNHA.[95] In a series of 219 patients with CTN (paroxysmal only), 28.3% had no imaging evidence of NVC,[96] and up to 17% of patients undergoing surgery for CTN had no NVC.[97,98] In patients with pain recurrence after initially successful microvascular decompression (MVD), there was no evidence of relapsed vessels causing renewed compression.[95] In cases of bilateral CTN, less than 50% of patients had imaging evidence of bilateral NVC.[96] Furthermore, 17% of age-matched CTN-free controls have imaging evidence of NVC.[99] CTN patients with no NVC are typically younger and 3 times more likely to be females,[100] suggesting that CTN with and without NVC may be discrete groups. Although NVC clearly plays a role in individual patients, at a population level the high prevalence of NVC and the rarity of CTN suggest that a finding of NVC in CTN may be insignificant. Once again we are faced with evidence that CTN is a far more complex disease (or cluster of diseases) than previously appreciated.

A review of published cases shows that only 17% of SUNCT/SUNA cases had NVC,[101] which is much lower than in CTN.[63,102,103] The incidence of NVC in asymptomatic patients is also around 17%, so the true significance of NVC in SUNHA is unclear. It seems that both in CTN and SUNHA we need to look elsewhere, such as gender, genetics, or other predisposing factors to explain the onset and maintenance of pain.

The most widely accepted theory of TAC pathophysiology is that they are caused by a hypothalamic abnormality leading to hypothalamic activation with secondary activation of the trigeminal autonomic reflex, via a trigeminal-hypothalamic pathway. This theory receives support from functional imaging that identified the hypothalamus as central to the pathophysiology of the TACs.[11,61,104,105] Similar imaging findings in SUNHAs provide justification for classifying these with the TACs.[61,106]

To our knowledge, however, there have been no reports of hypothalamic dysfunction in CTN. Hypothalamic stimulation was successful in a group of CTN patients with multiple sclerosis,[107] particularly for pain in the ophthalmic branch. However, it is unclear whether this is acting via hypothalamic modulation of the trigeminal nociceptive system or acting directly on the hypothalamus. It is also unclear how much we should derive from reports on CTN associated with multiple sclerosis, in terms of applicability of these mechanisms of CTN.

A number of cases have been described of SUNCT/SUNA with neurovascular compression, similar to that in CTN.[101] These findings add to the ongoing discussion of SUNCT/SUNA's relationship with CTN, and to the possibility that both entities represent a clinical spectrum. However the question arises as to whether NVC is an incidental finding (see above) or indeed the underlying pathophysiology in these cases.

It seems, therefore, that at the pathophysiologic level current data indicate important differences between CTN and SUNHA.

RESPONSE TO THERAPY

Pharmacological Interventions

CTN will usually respond to carbamazepine, whilst SUNCT/SUNA are reported to display resistance to a wide

range of drugs from their onset.[24] Interestingly, CTN with concomitant persistent facial pain also exhibits poor response to both pharmacologic and surgical treatments.[2,3,19,83-85] In our 2016 analysis of 81 CTN cases, a significant improvement was more frequent in the short attack duration CTN group (74%) than in the long attack group (50%).[19] The short attack group demonstrated a statistically significant association between poor treatment response and longer disease duration, with the presence of CAS and atypical pain descriptors for pain quality.[19] These features could fit a diagnosis of SUNHA or an atypical CTN. However, these patients may be better viewed as the "gray area" in a spectrum of patients that range from very typical CTN to very typical SUNHAs.

Carbamazepine is highly efficacious in CTN, but up to 30% of patients may be initially resistant and up to 50% become refractory to carbamazepine therapy.[42] Other drugs such as baclofen, gabapentin, oxcarbazepine, and topiramate have also been reported to be efficient in controlling CTN.[108]

About one third of previously misdiagnosed SUNCT cases respond partially to carbamazepine,[25] and there are more recent reports of good outcomes with oxcarbazepine.[109,110] To date, lamotrigine is considered the treatment of choice in SUNHA and is recommended as initial therapy.[26,111] Lamotrigine seems to be more effective in episodic SUNCT/SUNA than in the chronic form.[26] SUNCT but less so SUNA, responds to treatment with relatively more recent anticonvulsants such as topiramate.[24,25] Gabapentin seems to be effective for both SUNCT and SUNA.[45]

Many of the reports on treatment outcome in SUNHA patients are on preselected and biased groups that have failed previous treatments or have been misdiagnosed. Additionally, in view of the possible misdiagnosis of some CTN cases with lacrimation as a SUNHA and some SUNHA cases with a paucity of CAS and occurring in the lower face as CTN, one must question the reliability of drug studies in these cohorts. There have been no well-controlled studies examining the response of large numbers of SUNHA patients to standard anti-CTN therapies. It is therefore precarious to draw absolute conclusions on this.

Surgical Interventions

When pharmacological treatment of CTN fails, patients often proceed to ganglion level ablative procedures or microvascular decompression (MVD). Case reports of surgical MVD and percutaneous trigeminal ganglion compression for SUNCT have appeared.[112,113] In a series of nine SUNCT/SUNA patients, immediate and complete relief following MVD was obtained in six. This was sustained for a mean follow-up of 22 months.[114] In other cases series, 75% of patients subsequently treated with MVD achieved complete pain relief lasting up to 31 months. Others were treated by glycerol or radiofrequency rhizotomy and gamma knife radiosurgery with reasonable outcomes.[101]

Since in CTN, pain recurrence following successful MVD may occur in the absence of renewed NVC the possibility arises that the effects of MVD may be non-specific.

Could Tic and TAC Co-Occur?

The co-occurrence of CH and CTN in the same patients is termed cluster-tic syndrome (CTS). In most of these patients, CTN attacks are intimately related to CH activity. In a large series of CH patients, CTN was reported to occur ipsilaterally in 4.5%.[115] This high prevalence suggests that comorbidity is not by chance and supports the idea of a spectrum in clinical presentation and even pathophysiology between the CTN and some TACs.

Neck movements may precipitate pain in CTS (40%), and an atypical form of CTS has been described with very short attacks that make CTS disturbingly similar to PH and even SUNCT. Some patients with CTS may enjoy improvement in both CH- and CTN-related pain following CH treatment.[115] In CTS, both CH and CTN usually appear on the same side, and both respond favorably to carbamazepine therapy. Most CTS patients are females, and although onset may be at any age it seems slightly more common between 40 and 50 years.

Chronic paroxysmal hemicrania (CPH)-CTN syndrome has also been reported.[116-118] The classical characteristics of both pain entities occur together on the same side and may be controlled with indomethacin. Mixed attacks have also been described and may cause confusion with SUNCT, however the CPH-tic syndrome components are individually responsive to treatment.[116] The interpretation is that in some cases with a mixed CTN-SUNHA phenotype, this may be the representation of co-occurrence as in the above.

CONCLUSIONS

In summary, patients with a combination of features that present an overlap between classical trigeminal neuralgia (CTN) and short-lasting unilateral neuralgiform headache attacks (SUNHA) has been reported. Both entities can occur at the same age of onset, present with severe, unilateral trigeminal pain, are triggered by innocuous stimuli, and are accompanied by constant background pain and cranial autonomic signs (CAS). The complexity of this differential diagnosis is recognized by the ICHD-3 beta classification, which recommends giving both SUNHA and CTN diagnoses to such cases.[1] This overlap may reflect a spectrum of disease ranging from typical CTN attacks to typical SUNHAs with a mixed phenotype in the middle.

It is becoming increasingly clear that CTN is a more complex disease entity than previously appreciated. Historically, CTN was not considered to present with constant background

pain or CAS, nor was it accepted that the pain could wake patients. Clinically detectable sensory changes reported in CTN patients remain a contentious issue. However, reports of CTN with such varying signs and symptoms suggest an expanded clinical phenotype or possible subgroups.

Current data suggest a clinical continuum between CTN and SUNHA. SUNHA and CTN may be attributable to a unifying pathophysiological model characterized by different degrees of interaction between peripheral and central mechanisms. The number and type of clinical phenomena that develop may determine the diagnosis. Over time, a complex patient profile may develop which is harder to diagnose and responds poorly to pharmacological and/or surgical interventions.

Further longitudinal and larger multicenter patient trials with functional imaging studies are needed to address these questions. Due to the rarity of these entities, multicenter studies are essential to achieve a large sample size and to demonstrate the range of clinical phenotypes. In spite of the clinical and therapeutic overlap, there remains a lack of documented peripheral sensory neurophysiologic abnormalities in SUNHAs to suggest a neuropathic basis. Also, the similarities in functional imaging studies between SUNHAs and other TACs seem to point to a close relation with the neurovascular type TACs. More work will be needed to elucidate this relationship further.

Clinical Highlights

- There is a significant overlap between classical trigeminal neuralgia (CTN) and short-lasting unilateral neuralgiform headache attacks (SUNHA), at times with so much in common that a spectrum of disorders may exist.
- Both CTN and SUNHA can have the same age of onset, can present with severe, unilateral trigeminal pain, can be triggered by innocuous stimuli, and can be accompanied by constant background pain and cranial autonomic signs (CAS).
- The difficulty in diagnosis can also manifest in treatment. Traditionally, SUNHA responds to lamotrigine, gabapentin, and topiramate, while CTN responds to carbamazepine and oxcarbazepine, but one disorder can respond to the other set of medications.
- SUNHA and CTN may be attributable to a unifying pathophysiological model characterized by different degrees of interaction between peripheral and central mechanisms.

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