Trigeminal autonomic cephalalgia (TAC) is now an accepted clinical term, first proposed by Goadsby and Lipton, for a group of primary headaches with pain and autonomic involvement in the facial area of the trigeminal nerve. All these headache syndromes have two features in common: short-lasting, unilateral, extremely severe headache attacks accompanied by typical autonomic symptoms. The typical clinical features of the TACs are highly characteristic. To date, the following syndromes are accepted as belonging to the TACs:

- Episodic and chronic cluster headache (Table I)
- Episodic and chronic paroxysmal hemicrania (Table II)
- Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT syndrome) (Table III)

Why is it important for clinicians to know and recognize all the different types of TAC, given that they are relatively rare? First of all, these disabling conditions are easy to recognize. Second, they show an excellent, but highly selective, response to treatment. In most cases, a subclassification is possible and reasonable, because therapeutic regimens and responses differ. In 1997, Goadsby and Lipton documented a nosological analysis and definition of a group of short-lasting headache syndromes. These paroxysmal hemicranias are characterized by frequent, short-lasting attacks of unilateral pain, usually in the orbital, supraorbital, or temporal region. The pain is severe and is associated with autonomic symptoms such as conjunctival injection, lacrimation, nasal congestion, rhinorrhea, ptosis, and eyelid edema.

Goadsby and Lipton divided these short-lasting primary headache syndromes into those exhibiting marked autonomic activation and those without autonomic activation. Table IV summarizes a list of short-lasting headaches with autonomic symptoms. This group comprises chronic and episodic paroxysmal hemicrania, SUNCT syndrome, and cluster headache. The major clinical discriminating factor for the differential diagnosis of TACs is the relationship between duration and frequency of attacks: the forms in which pain is shorter lived are those with a higher frequency of daily attacks (see Fig. 1). These headache syndromes can be compared with other short-lasting headache disorders, such as hypnic headache, and with a chronic headache syndrome with milder autonomic features, known as hemicrania continua. Although these conditions are not currently classified as TACs, recent imaging data place hemicrania continua nearer to the TACs, and future work will probably do
Cluster Headache

Cluster headache is a relatively common condition by neurological standards, probably affecting about 1 in 1000 people, although compared to other more common primary headaches, such as migraine, it is clearly rare in clinical practice. Cluster headache is certainly the most prominent and most common of the TACs and is considered one of the most severe pain syndromes in humans—in fact, women have described the attacks as being worse than childbirth. A recent health-related quality of life study suggests that cluster headache has marked functional consequences, even when appropriate treatments are used, but this type of headache is still underdiagnosed and suboptimally managed in primary care.

The diagnosis of cluster headaches is exclusively a clinical task. The International Classification of Headache Disorders uses explicit diagnostic criteria (see Table I), which are “unambiguous, precise and with as little room for interpretation as possible.” The fact that at least 14 synonyms for cluster headache have been used in the past underlines the former lack of etiological understanding and demonstrates the importance of operational, hence explicit, diagnostic criteria for research and clinical practice (see http://www.i-h-s.org/). Cluster headache, in its typical form, is unmistakable. However, no single instrumental examination is able to define or differentiate idiopathic headache syndromes. Nevertheless, in the clinical setting, the use of neuroimaging techniques—such as computed tomography (CT), magnetic resonance imaging (MRI), and MR angiography—in headache patients varies widely. Electrophysiological and laboratory examinations, including examination of the cerebrospinal fluid, are not helpful. For the initial diagnosis and in the case of an abnormal neurological examination, a cranial CT scan and a cranial MRI should be considered in order to exclude abnormalities of the brain. Particularly in older patients, mass lesions or malformations in the midline have been described in association with symptomatic cluster headache.

Clinical Appearance

The stereotypical attacks may strike up to eight times a day, are relatively short-lived, and are characterized by strictly unilateral severe head pain accompanied by autonomic phenomena. Only in approximately 15% of cases is there a shift from one side of the head to another. In contrast to migraineurs, cluster headache patients are restless and prefer to pace about or sit and rock back and forth. Some patients will exert pressure on the painful area with a hand over the affected eye and temple. Many will isolate themselves during the attack or leave the house to get into the cold fresh air. Patients tend to become aggressive during an attack.

The unilateral autonomic symptoms such as ptosis, miosis, lacrimation, conjunctival injection, rhinorrhea, and nasal congestion occur only during the pain attack and are ipsilateral to the pain, indicating parasympathetic hyperactivity and sympathetic impairment. In some patients the signs of sympathetic paralysis (miosis and ptosis) persist indefinitely but intensify during attacks. Sweating and cutaneous blood flow also increase on the painful
The episodic variant, little is known about rhythmicity in chronic cluster headache. A recent case report in a secondary chronic cluster headache presented with three atypical cluster headaches, each with distinct autonomic symptoms, and in treatment options (see Table IV).

Another clinical landmark of the syndrome is the circadian rhythmicity of the relatively short-lived (15–180-minute) painful attacks. In the episodic form, attacks occur daily for some weeks followed by a period of remission. In the chronic form, attacks occur without significant periods of remission or with annual remission periods of less than 1 month. On average, a cluster period lasts 6–12 weeks, while remissions can last up to 12 months.

While circadian and circannual rhythmicity are characteristic of the episodic variant, little is known about rhythmicity in chronic cluster headache. A recent case report in a secondary chronic cluster headache showed that even in the chronic form, there was a distinct circadian and semi-circannual rhythmicity over time. Infra- and supra-annual exacerbations over several weeks occurred independently from a 12-month cycle.

Recognition of the periodicity of cluster headache is important for clinicians, because depending on the level of activity of the disease, a preventive medication may be efficient at some times and not at others. This statement implies that a lack of effect from preventive medications should not be misinterpreted as a failure; these prophylactic drugs may very well be effective when the activity of the disease levels out again. In addition, a “clockwise” circadian rhythmicity of attacks and an individual circannual preponderance should be considered as a hallmark for cluster headache. Sjaastad suggested that episodic and secondary chronic cluster headache have only minor differences and display smooth transitions, while primary chronic cluster headache is a separate entity lacking the criterion of clustered attacks. A primary cluster headache is defined as being unrelated to any morphological cause (the patient’s medical history and physical and neurological diagnosis are normal), whereas a secondary cluster headache is a headache with all the features of a cluster headache that is the result of another disorder that is a known cause for this type of headache. It is not clear whether that is true, but primary chronic cluster headache seems to be medically intractable more often than secondary cluster headache. When chronic cluster headache is unresponsive to medical treatments, it becomes a serious problem, and even surgical options may need to be considered.

### Differential Diagnosis

All headache syndromes with short-lasting, unilateral, severe headache attacks and typical autonomic accompanying symptoms need to be considered (e.g., paroxysmal hemicrania and SUNCT). However, these syndromes differ in duration, in the frequency and rhythmicity of attacks, in the intensity of pain and autonomic symptoms, and in treatment options (see Table IV). There are reports of aura in cluster headache and even reports of a “hemiplegic cluster.” There seem to be some cases of cluster headache without headache, cluster headache without autonomic symptoms, and even bilateral cases. In a series of well-observed case reports presenting three atypical cluster headaches, the authors suggest that as more cluster patients are seen by headache specialists, new forms of this well-defined primary headache syndrome will be identified. However, the concept of trigemino-autonomic syndromes is certainly useful for clinicians seeking a pathophysiological understanding of the primary neurovascular
headaches, and it allows us to place the various treatments aimed at treating or preventing these headaches into context.

With a prevalence of approximately 0.1%, cluster headache mostly affects men. The attacks occur regularly, and their timing seems to be related to the sleep-wake cycle. Attacks most commonly appear in cluster periods (episodic cluster headache) lasting from a week to several months. The periods are separated by clinical remissions of at least 2 weeks. About 15–20% of patients suffer from chronic symptoms without remissions (chronic cluster headache). The most salient feature of cluster headache is the reported seasonal variation and the clockwise regularity of the headache attacks. A whole range of circadian irregularities in hormone levels have been reported in cluster headache patients. Melatonin in particular is a marker of the circadian system, and a blunted nocturnal peak melatonin level and complete loss of circadian rhythm have been reported in cluster headache patients. Although for hemicrania continua it is clear that there is pain between attacks, this interictal pain feature is now well recognized in the other TACs. In a cohort of 52 patients with SUNCT or SUNA (short-lasting neuralgiform headache with autonomic symptoms), 22 patients had interparoxysmal pain. It may be that interparoxysmal pain and allodynia in TACs represent a coexistence of the TAC pathophysiology with migraine. The clinical importance is that one needs to be aware of these overlaps so as to identify the major presenting problem that requires treatment.

**Fig. 2.** Diagram of the therapeutic options in the treatment of trigemino-autonomic headaches, divided into acute and abortive treatment. For dosages, please refer to the text.

**Treatment**

Fig. 2 outlines the therapeutic options in the treatment of trigemino-autonomic headaches, divided into acute and abortive treatment.

**Aborting Acute Attacks**

Subcutaneous sumatriptan and oxygen inhalation are first-line treatments for an acute cluster headache attack. Other agents with some evidence of effectiveness include ergots and lidocaine.

**Oxygen:** Recently, a placebo-controlled study confirmed the clinically well-known fact that oxygen inhalation is safe and effective for aborting cluster headache. Oxygen (100%) is administered via a nonrebreathing facial mask with a flow rate of at least 8–10 L/min. Oxygen inhalation should continue for 20 minutes with the patient in an upright sitting position. Oxygen is generally safe and without side effects. However, patients with severe chronic obstructive pulmonary disease should not be treated with inhaled oxygen because of the risk for developing severe hypercapnia and CO$_2$ narcosis. Higher oxygen flow rates, up to 15 L/min, may sometimes be effective when standard rates are not. From a practical standpoint, it is reasonable to increase the flow rate if a lower rate is ineffective, as a higher flow rate does not increase the risk of side effects.

**Triptans.** In double-blind, placebo-controlled trials involving a combined total of 183 patients with cluster headache, subcutaneous

**Cluster Headache**

**Paroxysmal Hemicrania**

**SUNCT Syndrome**

**Abortive**

100% Oxygen
Sumatriptan, s.c.
Zolmitriptan, nasal
Lidocaine, local

**Preventive**

Drug Combinations
Verapamil + Lithium
Verapamil + Methysergide
Verapamil + Topiramate
Verapamil + Valproic Acid
Verapamil + Lithium + Topiramate

**Occipital Block**

Stimulation of the Greater Occipital Nerve
Hypothalamic Deep Brain Stimulation
Sphenopalatine Ganglion Stimulation

**Abortive**

Verapamil
Topiramate
Lithium
Methysergide

No effective therapy known

**Preventive**

Indomethacin

No effective therapy known

**Abortive**

Gabapentin

**Preventive**

Lamotrigine

**Abortive**

Topiramate

**Preventive**

Hypothalamic Deep Brain Stimulation?
sumatriptan (6 mg) was effective (relieving pain within 20 minutes) in about 75% of patients. It is safe, with no evidence of tachyphylaxis or rebound in most patients, even after frequent use. Intranasal sumatriptan or zolmitriptan is also effective for aborting acute cluster headache attacks.

**Lidocaine.** Small observational studies suggest that intranasal lidocaine is effective in at least one-third of patients, although the degree of benefit is modest. Intranasal lidocaine (1 mL) is administered ipsilateral to the pain in a 4–10% solution. The neck should be in extension by 45°, with the head rotated toward the symptomatic side by 30–40°.

**Ergots.** Oral ergotamine has been used as a treatment for cluster headache attacks since the 1940s. Oral ergotamine is effective for acute cluster headache, based upon clinical experience, but modern trials are lacking.

**Preventive Treatment**

Preventive therapy should be started as soon as possible at the onset of a cluster episode. The goal is to suppress attacks over the expected duration of the cluster period. An effective preventive regimen is of utmost importance because patients typically have one to eight cluster headaches a day, and repeated use of abortive medications may result in toxicity or a rebound effect.

**Verapamil.** Verapamil is the agent of choice for the preventive therapy of cluster headache. Other agents that may be effective include glucocorticoids, lithium, topiramate, and methysergide. When chronic cluster headache is unresponsive to medical treatments, surgical options can be considered. However, destructive procedures aimed at the sensory trigeminal nerve or autonomic pathways are generally unproven. Occipital nerve stimulation, deep brain stimulation, and stimulation of the sphenopalatine ganglion appear promising, but are investigational.

**Glucocorticoids.** Glucocorticoids have not been evaluated by rigorous randomized controlled trials for the treatment of cluster headache. Consequently, there are no data favoring one regimen of glucocorticoid administration over another. The usual recommendation is to start prednisone at 60 to 100 mg once a day for at least 5 days, and then taper by decreasing the dose by 10 mg every day.

**Lithium.** Because lithium has a narrow therapeutic window, it is generally used for patients with chronic cluster headache only when other drugs are ineffective or contraindicated. The initial dose of lithium should be 20 mg/kg, and the typical maintenance dose is 900 to 1200 mg/day. Lithium plasma levels should be monitored and kept between 0.6 and 1.2 mmol/L.

**Methysergide.** There are no randomized controlled trials evaluating methysergide for cluster headache. Methysergide is usually started at 1 mg daily. The dose is gradually increased as tolerated to an effective amount, which for most responders is in the range of 4 to 12 mg daily, given in divided doses.

**Topiramate.** Topiramate is an effective add-on medication for cluster headache prevention, most often in combination with verapamil. This strategy can sometimes be used to avoid the need for high-dose verapamil monotherapy or long-term glucocorticoid treatment. The recommended starting dose of topiramate is 25 mg/day. It is titrated at weekly intervals in 25-mg increments according to clinical response and tolerance, up to the recommended daily total of 100 mg/day given in two divided doses.

**Paroxysmal Hemicrania**

**Clinical Appearance**

Paroxysmal hemicrania was first described by Sjaastad and Dale (for a review see Dodick) and is characterized by relatively short bouts of severe unilateral pain in the orbital and temporal area. The typical attack duration is 10–20 minutes, and the typical frequency is more than 5 attacks per day, but there are reports of between 1 and 40 attacks per day. The age of onset is usually in the twenties, with a 3:1 female to male ratio. As in the case of cluster headache, a chronic and an episodic form have been described, and the syndrome also conveys a distinctive temporal pattern. The pain is associated with at least one autonomic symptom, such as ipsilateral conjunctival injection and tearing with

<table>
<thead>
<tr>
<th>Table II</th>
<th>Diagnostic criteria for paroxysmal hemicrania</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. At least 20 attacks fulfilling criteria B–D</td>
<td></td>
</tr>
<tr>
<td>B. Attacks of severe unilateral orbital, supraorbital or temporal pain lasting 2–30 minutes</td>
<td></td>
</tr>
<tr>
<td>C. Headache is accompanied by at least one of the following:</td>
<td></td>
</tr>
<tr>
<td>1. Ipsilateral conjunctival injection and/or lacrimation</td>
<td></td>
</tr>
<tr>
<td>2. Ipsilateral nasal congestion and/or rhinorrhea</td>
<td></td>
</tr>
<tr>
<td>3. Ipsilateral eyelid edema</td>
<td></td>
</tr>
<tr>
<td>4. Ipsilateral forehead and facial sweating</td>
<td></td>
</tr>
<tr>
<td>5. Ipsilateral miosis and/or ptosis</td>
<td></td>
</tr>
<tr>
<td>D. Attacks have a frequency above 5 per day for more than half the time, although periods with lower frequency may occur</td>
<td></td>
</tr>
<tr>
<td>E. Attacks are prevented completely by therapeutic doses of indomethacin</td>
<td></td>
</tr>
<tr>
<td>F. Attacks are not attributed to another disorder</td>
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</tbody>
</table>
nasal congestion and rhinorrhea. The syndrome’s typical description as a women’s problem seems incorrect from a substantial cohort that has recently been reported.²⁷

The syndrome is also characterized by its complete response to indomethacin. Although this response is exceptional and long-lasting, patients who develop gastrointestinal problems, notably peptic ulcer disease, when taking indomethacin represent a substantial challenge. Some such patients have responded to cyclooxygenase-2-selective inhibitors, and others seem to benefit from gabapentin. Even if indomethacin is effective, it may be worth trying gabapentin because it has a better side-effect profile.

**Differential Diagnosis**

All headache syndromes with short-lasting, unilateral, severe headache attacks and typical autonomic accompanying symptoms (e.g., cluster headache and SUNA/SUNCT) need to be considered. The hallmarks in differential diagnosis are the duration of the attacks and a complete response to indomethacin.

**Treatment**

By definition, indomethacin in a daily dose of up to 200 mg is effective in all published cases.²⁸ Alternatively, gabapentin, verapamil, and nonsteroidal anti-inflammatory drugs (NSAIDs) can be tried. Since efficacy of indomethacin is a diagnostic criterion, no placebo-controlled trials exist. Indomethacin should be administered in three or more doses per day because of its short half-life of 4 hours. Many patients need a high dose of indomethacin only in the first few weeks of treatment, and then a lower dose can be tried. Very rarely, doses higher than 200 mg per day are required. Gastrointestinal discomfort and even bleeding are major side effects. Therefore, a proton pump inhibitor should be given in addition.

**SUNCT Syndrome**

**Clinical Appearance**

Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) is among the rarest of idiopathic headache syndromes and is characterized by an extremely high frequency of attacks (up to 200 attacks/day), with less severe pain than other TACs but marked autonomic activation during attacks. It has been suggested that the SUNCT syndrome may be a subtype of short-lasting unilateral neuralgiform headache attacks with cranial autonomic features (SUNA). Even though there are distinct clinical differences, such as the frequency and duration of attacks and the different approach to treatment, many of the basic features of SUNCT, such as episodic attacks, autonomic symptoms, and unilateral, are shared by other headache types, including cluster headache and chronic paroxysmal hemicrania. These common features suggest a pathophysiological similarity to those syndromes and has prompted the suggestion to unify them on clinical grounds as trigeminal-autonomic cephalgias (TACs). The paroxysms of pain usually last between 5 and 250 seconds, although longer, duller interictal pains have been reported. Patients can have up to 30 episodes per hour, although it is more usual to have 5–6 episodes per hour. The frequency may also vary between bouts. The conjunctival injection seen with SUNCT is often the most prominent autonomic feature, and tearing may also be obvious.

**Differential Diagnosis**

The major differential diagnosis involves trigeminal neuralgia. The most important clinical signs pointing toward SUNCT/SUNA and against trigeminal neuralgia include the prominent distribution of pain in the ophthalmic division of the trigeminal nerve, the triggering of attacks by cutaneous stimuli, and the lack of a refractory period to these triggers. In contrast to paroxysmal hemicrania, there is no reproducible indomethacin effect in SUNCT/SUNA, and in contrast to cluster headache, there is no important effect of oxygen, sumatriptan, or verapamil. For practical reasons, indomethacin should be tried first in all extremely short-lasting headaches, before trying lamotrigine or carbamazepine.

**Hemicrania Continua**

Hemicrania continua is currently not recognized as belonging to the TACs but has been grouped into section 4 of the International Headache Society classification.¹ However, many clinical signs as well as functional imaging point toward including hemicrania continua into the TAC section, so we are including it here for completeness. Hemicrania continua is characterized by a continuous, unilateral headache that varies in intensity, waxing and waning without disappearing completely. The International Headache Society definition states that the headache is side-locked,
meaning that it does not change sides. Usually there are mild autonomic symptoms such as lacrimation, conjunctival injection, nasal symptoms, and ptosis/miosis, and the syndrome typically responds well to indomethacin.

Hemicrania continua is sometimes misdiagnosed as half-sided tension-type headache or chronic migraine. Hemicrania continua is probably underdiagnosed, but the absolute requirement for an indomethacin effect is helpful in distinguishing it from other primary headaches. However, cases with bilateral pain have been reported, and interestingly, typical migraine features of nausea, photophobia, and phonophobia, in addition to the ipsilateral cranial autonomic symptoms, may arise with exacerbations. In general terms, the background pain of hemicrania continua is more severe than the interparoxysmal pain of the other TACs, and the worsenings in hemicrania continua are longer than the paroxysms of the other TACs. This feature is particularly important in differentiating hemicrania continua from paroxysmal hemicrania.

<table>
<thead>
<tr>
<th>Table IV</th>
<th>Comparison of cluster headache with related headache syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cluster Headache</td>
</tr>
<tr>
<td><strong>Epidemiology</strong></td>
<td></td>
</tr>
<tr>
<td>Gender (male : female)</td>
<td>3:1</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0.9%</td>
</tr>
<tr>
<td>Age of onset</td>
<td>28–30 yr</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td></td>
</tr>
<tr>
<td>Quality</td>
<td>Boring, throbbing</td>
</tr>
<tr>
<td>Intensity</td>
<td>Extremely high</td>
</tr>
<tr>
<td>Localization</td>
<td>Periorbital</td>
</tr>
<tr>
<td>Duration of attack</td>
<td>15–120 min</td>
</tr>
<tr>
<td>Frequency of attack</td>
<td>1–8/d</td>
</tr>
<tr>
<td><strong>Autonomic symptoms</strong></td>
<td>++</td>
</tr>
<tr>
<td>Circadian rhythmicity</td>
<td>+</td>
</tr>
<tr>
<td><strong>Alcohol trigger</strong></td>
<td>++</td>
</tr>
<tr>
<td>Treatment of choice, acute</td>
<td>100% oxygen, 15 L/min; intranasal lidocaine; sumatriptan s.c.</td>
</tr>
<tr>
<td>Treatment of choice, preventive</td>
<td>Verapamil, lithium carbonate, corticosteroids, topiramate, methysergide</td>
</tr>
<tr>
<td>Second-line treatment and occasional reports</td>
<td>Valproic acid, ergotamine, melatonin, pizotifen, indomethacin</td>
</tr>
</tbody>
</table>

Source: Modified from May.

*Abbreviations and symbols: SUNCT = short-lasting unilateral neuralgiform headache with conjunctival injection and tearing. +, positive; –, nonexistent; (+), probable; (-) rare.*

**Treatment**

Just as with paroxysmal hemicrania, indomethacin is the drug of first choice, in a daily dose of up to 200 mg. Alternatively, gabapentin, caffeine, and NSAIDs (e.g., naproxen) can be tried.²⁸

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