

# Trigeminal autonomic cephalalgias or migraine?

Anna Sundholm  
MD, PhD  
ME Neurologi

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# Diagnosics migraine vs TAC's

## 1.1 Migraine without aura

- A. At least five attacks fulfilling criteria B-D
- B. Headache attacks lasting 4-72 hours (when untreated or unsuccessfully treated)
- C. Headache has at least two of the following four characteristics:
  - 1. unilateral location
  - 2. pulsating quality
  - 3. moderate or severe pain intensity
  - 4. aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
- D. During headache at least one of the following:
  - 1. nausea and/or vomiting
  - 2. photophobia and phonophobia
- E. Not better accounted for by another ICHD-3 diagnosis.

3

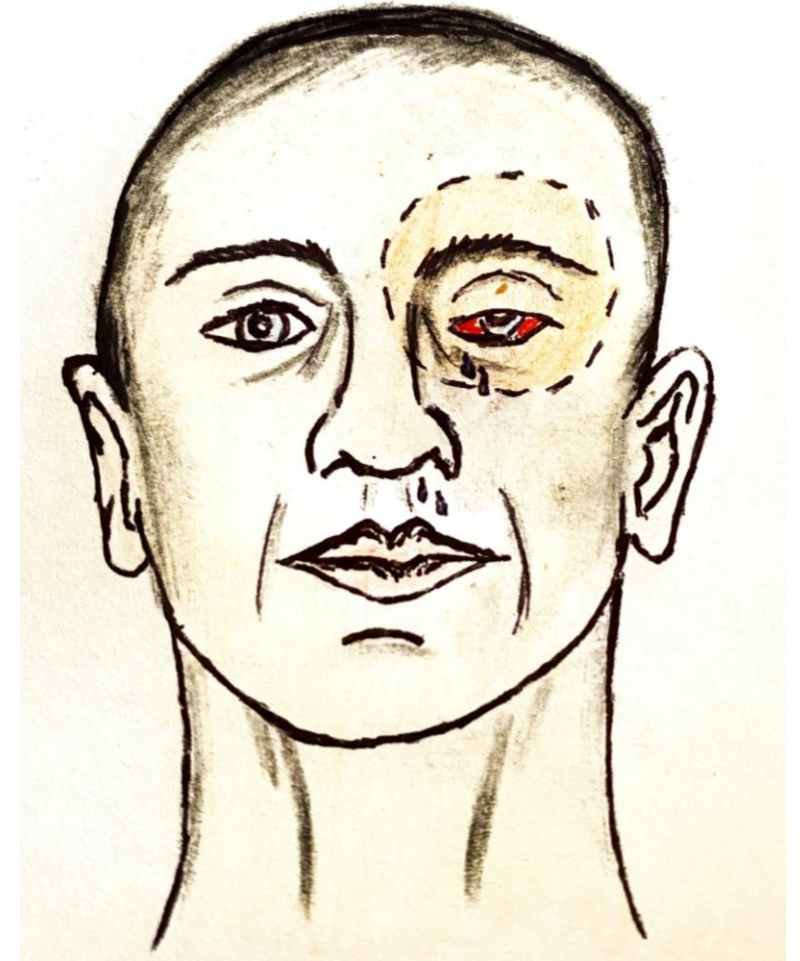
## 3.1 Cluster headache

- A. At least five attacks fulfilling criteria B-D
- B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes (when untreated)
- C. Either or both of the following:
  - 1. at least one of the following symptoms or signs, ipsilateral to the headache:
    - a) conjunctival injection and/or lacrimation
    - b) nasal congestion and/or rhinorrhoea
    - c) eyelid oedema
    - d) forehead and facial sweating
    - e) miosis and/or ptosis
  - 2. a sense of restlessness or agitation
- D. Occurring with a frequency between one every other day and 8 per day
- E. Not better accounted for by another ICHD-3 diagnosis.



# CAS = cranial autonomic symptoms

- Lacrimation
- Conjunctival injection
- Rhinorrhea
- Nasal congestion
- Forehead and facial sweating
- Ptosis
- Miosis
- Eyelid edema



As classified by the IHS classification. Cephalalgia. 2018; 38: 1-211

# Frequency of cranial autonomic symptoms in migraine – review of the literature

- Forehead Sweating (12,4 - 58,1)
- Facial Flushing (3,5 - 50)



- Miosis (1,9 - 6,3)
- Lacrimation (12 - 78)
- Congjuntival Injection (5,6 - 64)
- EyeLid Edema and Ptosis (4,7 - 66,2)
- Grittiness and Scratchiness (15,1 - 22)



- Rhinorrhea (3 - 50)
- Nasal Congestion (11 - 43)
- Red Ear (21,3)
- Aural Fullness (7,4 - 36,6)



- Throat Swelling (1,6)
- Voice Change (-)



Cascio S L et al. Cranial Autonomic Symptoms and Migraine: What Relationship and What Meaning? A Review. *J. Integr. Neurosci.* **2022**, 21(6), 166.

Danish population-based sample (N= 62,677) using both questionnaire-based diagnosis (N = 12,620) and interview-based diagnosis validation (N = 302)

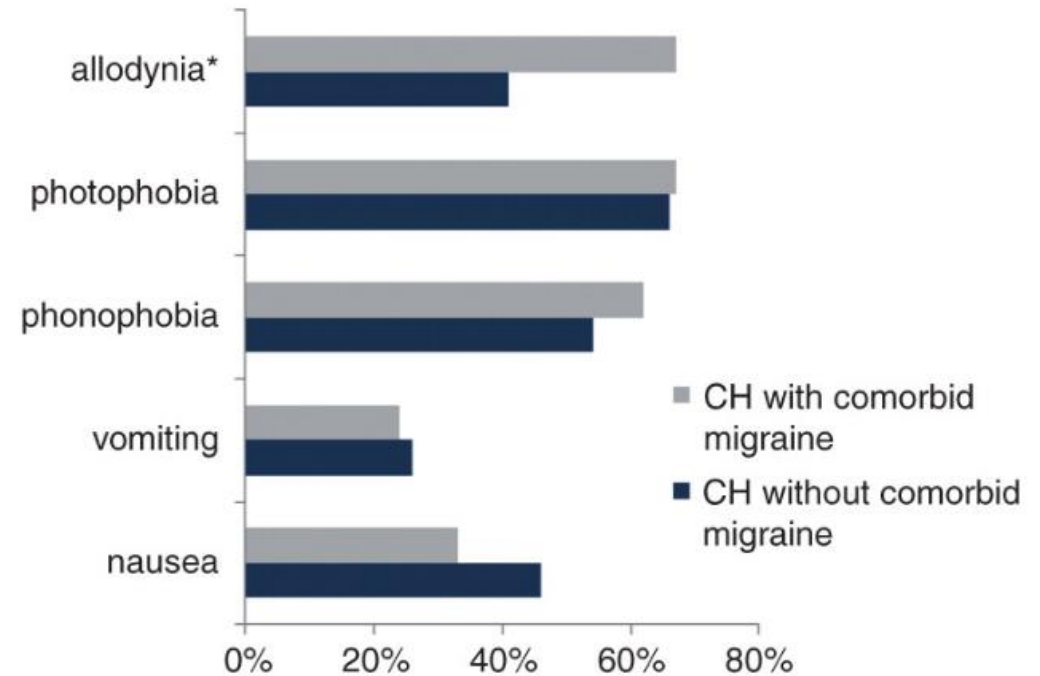
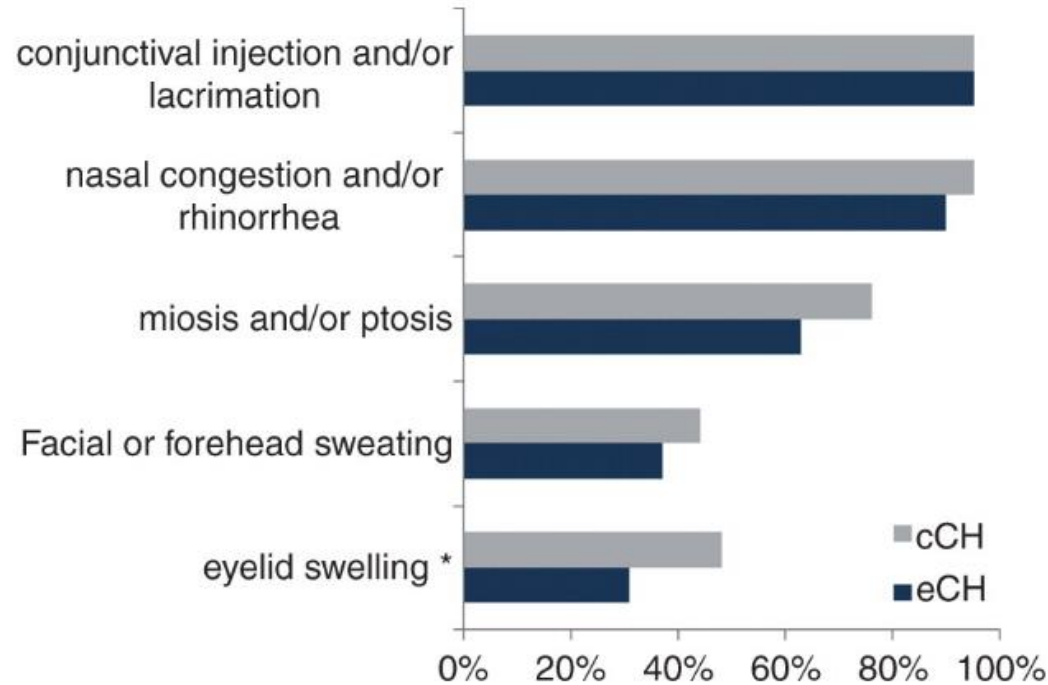
Cranial autonomic symptoms	Prevalence of CAS during migraine attacks in the DaMP cohort		Prevalence of CAS during cluster headache attacks in DHC <sup>24</sup>
	Diagnostic questionnaire (N = 12,620) n (%)	Semi-structured validation interview (N = 302) n (%)	Questionnaire (N = 57) n (%)
Facial/forehead sweat <sup>a</sup>	4,909 (39)	59 (20)	94 (19)
Lacrimation	3,031 (24)	40 (13)	272 (54)
Ptosis	1,747 (14)	31 (10)	224 (45)
Conjunctival injection	1,615 (13)	50 (17)	241 (48)
Rhinorrhea	1,439 (11)	16 (5)	183 (37)
Nasal congestion	1,362 (11)	23 (8)	200 (40)
Miosis	752 (6)	19 (6)	51 (10)
Number of symptoms			
≥ 1 CAS	7,179 (57)	132 (44)	408 (82)
≥ 2 CAS	3,968 (31)	66 (22)	–
≥ 3 CAS	2,153 (17)	30 (10)	
≥ 4 CAS	1,018 (8)	6 (2)	
≥ 5 CAS	396 (3)	3 (1)	
≥ 6 CAS	118 (1)	1 (0.3)	
= 7 CAS	23 (0.2)	0 (0)	

CAS: cranial autonomic symptoms; DaMP: Danish Migraine Population cohort; DHC: Danish Headache Center.

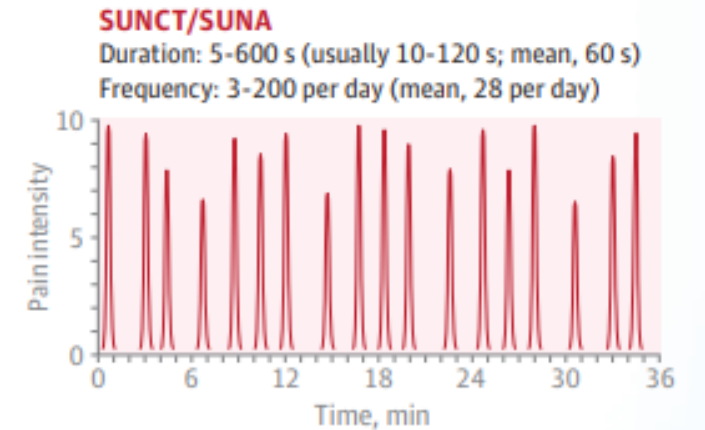
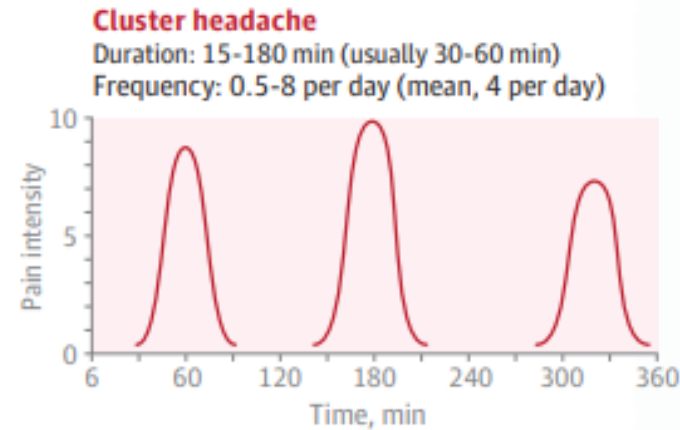
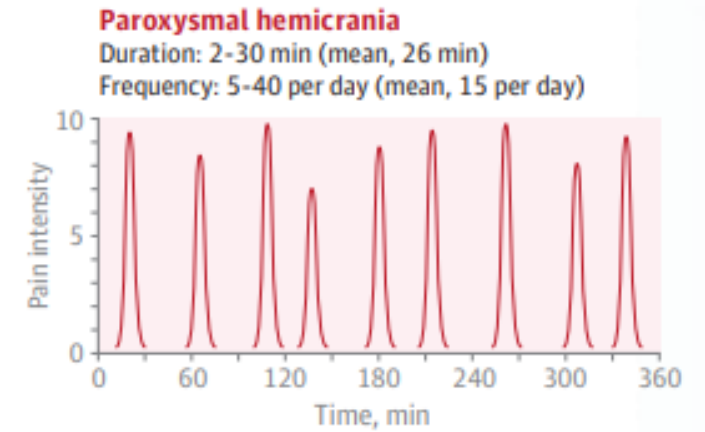
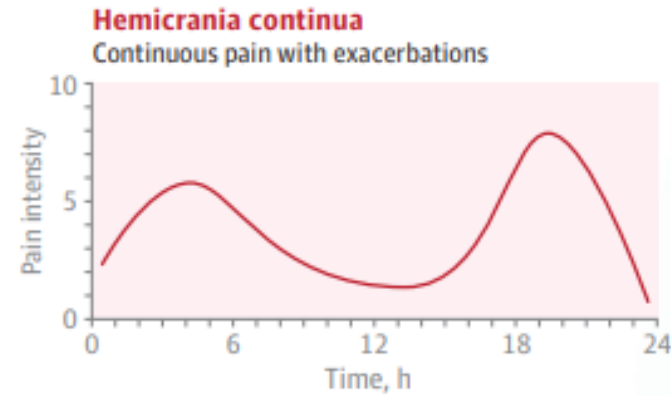
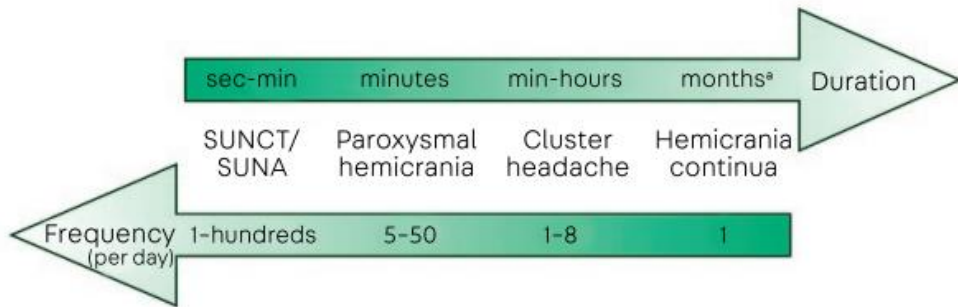
<sup>a</sup>In the DaMP cohort the participants answered yes to having either or both facial and forehead sweat. In the DHC cluster headache cohort the prevalence refers to participants who answered yes to having both facial and forehead sweat.

# Study in Essen Germany on cluster patients evaluating clinical features in cluster attacks.

209 consecutive cluster headache patients (144 eCH, 65 cCH)  
male : female ration 3.4:1



# Differentiate TAC's



Diener HC et al. Management of Trigeminal Autonomic Cephalalgias Including Chronic Cluster: A Review. JAMA Neurol. 2023.

Mark J. Burish. Cluster Headache and Other Trigeminal Autonomic Cephalalgias. Continuum 2018



# Sex difference and bout length in cluster headache

**Table 2** Demographic and Clinical Characterization of Swedish Patients With Cluster Headache

	All	Male	Female	p Value
Number of individuals (% of all)	874	575 (65.8)	299 (34.2)	—
Interview age (y)	50.5 ± 14.3 (17–83)	51.3 ± 13.9 (17–83)	49.0 ± 15.0 (17–83)	<b>0.028<sup>c</sup></b>
Attack duration (min)				0.10
15–30	18.4	17.5	20.2	
30–120	50.9	53.7	45.7	
120–180	17.7	17.1	18.7	
>180	13.0	11.6	15.4	
Bout length (mo)				<b>0.003<sup>d</sup></b>
0–1	28.5	29.8	26.0	
1–2	30.7	31.9	28.3	
2–4	21.1	22.5	18.3	
4–7	6.2	5.2	8.0	
7–12	4.9	4.2	6.3	
>12	8.7	6.4	13.0	
Pain intensity* <sup>a</sup>	9.26 ± 0.98 (5–10)	9.24 ± 1.01 (5–10)	9.30 ± 0.95 (6.5–10)	0.62
Associated symptoms				
Conjunctival injection	58.1	59.8	54.8	0.17
Lacrimation	74.7	75.0	74.2	0.87
Ptosis	51.6	47.0	60.5	<b>0.0002<sup>e</sup></b>
Nasal congestion	50.8	49.6	53.2	0.32
Rhinorrhea	47.3	45.7	50.2	0.23
Restlessness	48.4	45.6	53.8	<b>0.022<sup>c</sup></b>
Nausea* <sup>a</sup>	22.8	20.1	27.1	0.16

Fourier C, Ran C, Steinberg A, Sjöstrand C, Waldenlind E, Belin AC. Sex differences in clinical features, treatment, and lifestyle factors in patients with cluster headache. *Neurology*. 2023;100(12):e1207-e1220.

# Why could CAS+ be of importance in migraine?

- Differential diagnosis consideration?
- More severe form?
- Treatment response?

# Treatment response to triptans - better in those with CAS+?

Evaluating 10 responders and 10 non responders to rizatriptan (previously treatment naive patients)

	Before rizatriptan administration		1 h		2 h	
	Responders <i>n</i>	Non-responders <i>n</i>	Responders <i>n</i>	Non-responders <i>n</i>	Responders <i>n</i>	Non-responders <i>n</i>
Associated symptoms						
Nausea	8	7	3	7	1	8
Vomiting	2	3	1	3	0	2
Photophobia	9	7	4	8	2	8
Phonophobia	8	6	3	6	2	6
Autonomic signs or symptoms						
Lacrimation	3	0	1	0	0	0
Conjunctival injection	5	0	3	0	1	0
Eyelid oedema	3	0	2	0	1	0
Nasal obstruction	2	0	2	0	0	0

# Associated features in responders to frovatriptan

- 29 patients enrolled. 30% pain free after 2 hours (responders)

## **Associated to good response to treatment:**

- unilateral pain
- presence of phonophobia
- presence of one or more cranial autonomic symptoms
- presence of one or more premonitory symptom

## **Associated to not as good response to treatment:**

- severe pain
- nausea
- vomiting

# Other features observed in the literature

- Anecdotal reports of
  - oxygen response in CAS+ severe migraine attacks
  - CAS+ has been proposed a possible positive predictor of positive treatment response with Onabotulinum toxin A treatment in CM
- CAS+ seems more common in CM compared to EM
  - Increased frequency play a role?
- Studies tend to suggest that CAS+ migraineurs have more severe attacks, more frequent and perhaps longer?

Jürgens TP et al. Cephalalgia 2013; 33:65-67  
Barbanti P et al. Journal of Pain Research 2017;10:2319-2329  
Barbanti P et al. European Journal of Neurology 2018;25:e40  
Cortez MM et al. Journal of Neuro-Ophthalmology 2020;40:67-73  
Cascio S L et al. J. Integr. Neurosci. 2022, 21(6), 166.

# *Proposed diagnostic appendix criteria for Migraine with CAS*

## **Proposed criteria for migraine with CAS+ for use in genetic and epidemiological studies**

- A. Attacks fulfilling the diagnostic criteria for:
  - 1.1 Migraine without aura and/or
  - 1.2 Migraine with aura
- B. Data obtained by questionnaire
- C. At least two of the following fully reversible autonomic symptoms have been present during migraine attack:
  - 1. Conjunctival injection
  - 2. Lacrimation
  - 3. Nasal congestion
  - 4. Rhinorrhea
  - 5. Forehead or facial sweating
  - 6. Miosis
  - 7. Ptosis
  - 8. Eyelid oedema
- D. Not better accounted for by another ICHD-3 diagnosis

## **Proposed criteria for migraine with CAS+ for use in clinical and pathophysiological studies**

- A. Attacks fulfilling the diagnostic criteria for:
  - 1.1 Migraine without aura and/or
  - 1.2 Migraine with aura
- B. During at least one third of the attacks, symptoms according to criterion C have been present. Data must be obtained by semi-structured interview
- C. At least two of the following fully reversible autonomic symptoms:
  - 1. Conjunctival injection
  - 2. Lacrimation
  - 3. Nasal congestion
  - 4. Rhinorrhea
  - 5. Forehead or facial sweating
  - 6. Miosis
  - 7. Ptosis
  - 8. Eyelid oedema
- D. Not better accounted for by another ICHD-3 diagnosis